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JUNE 1955

VOLUME 73 NUMBER 6

A PRELIMINARY NOTE ON THE USE OF CHLORPROMAZINE WITH NEUROPSYCHIATRIC DISORDERS — R. C. COWDEN, Ph.D., ET AL.

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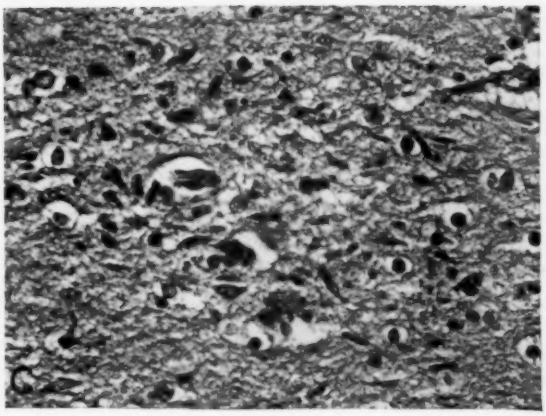

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Compulsive Eye Opening and Associated Phenomena

LOUIS BERLIN, M.D., Mount Vernon, N. Y.

During the course of examination of a patient who had recently sustained a cerebral thrombosis with resultant left hemiplegia, hemisensory defect, and hemianopsia, it was observed that the patient failed to keep his eyes closed despite repeated urging by the examiner. This failure to keep his eyes closed was at first interpreted as a refusal to cooperate in the examination, but it was subsequently realized that during the waking state the patient could not maintain his eyes closed; instead, there was an irresistible compulsion to reopen the eyes after they had been closed voluntarily. It was then found that there was a triad of signs related to facial and mouth movements. This consisted of inability to maintain the eyes closed, the mouth open, or the tongue protruded for periods up to 30 seconds, despite the adequate strength of the muscles participating in these movements.

COMPULSIVE EYE OPENING

The inability to keep the eyes closed was the first of these phenomena to be recognized. The instruction to the patient was to close his eyes and maintain them closed until told to open them. There were various degrees of inability to carry out this instruction. The most obvious impairment was evident in the spontaneous opening of both eyes within 10

From the Department of Medicine (Neurology), New York Hospital-Cornell Medical Center, New York, and the Neurology Section, Veterans Administration Hospital, Bronx, N. Y.

Fig. 1.—Inability to keep the eyes closed for more than five seconds in a patient with a right middle cerebral artery thrombosis sustained two months previously. Note that the left eye opens first. From a film taken at 8 frames/second.

to 30 seconds after closure of the lids (Fig. 1). The patients who exhibited this response often practiced closing their eyes and later related that, despite this practice, they nevertheless found themselves unable to resist the tendency of their eyelids to open. Although this inability was most consistently demonstrated in patients with recent lesions, it was occasionally evident two years after the onset of the lesion.

As some patients improved, the phenomenon of compulsive eye opening was modified, so that first the eye on the side of the hemiparesis (usually the left) would open and then the opposite eye would open. There then might follow another phase of the improvement, during which only the left eye would open completely, while the right eyelids were fluttering as if it were an effort to keep them shut. At this point the patient might be unaware that one eye was open, and, denying that it was open, proudly assert that he had now achieved the ability to keep both eyes closed. This denial of the opening of the eye was expressed by subjects who had manifested previously a denial of their left hemiplegia and who had associated severe hemisensory or hemianoptic defects.

Finally, some weeks or months after the onset of their illness, patients who had passed through these stages were able to keep their eyes closed for over 30 seconds. However, while the lids were closed, they quivered as if they were about to open.

It should be noted that all of these patients slept with their eyes closed. Both eyes closed readily when either was painfully stimulated to cause blinking. Furthermore, it was observed that the eyes tended to open and to remain open in five patients while they were being photographed under bright lights, despite the usual disposition to squint and close the eyes under these circumstances.

Fig. 2.—Inability to keep the tongue protruded for more than five seconds. From a film taken at 8 frames/second.

COMPULSIVE MOUTH CLOSURE

These patients, who had the inability to keep their eyes open, could not sustain a position in which the mouth was open and/or the tongue protruded. Instead, after the tongue was protruded upon command, it soon returned to its resting position in the mouth (Fig. 2). However, there might be a few intermittent forward movements in an abortive effort to maintain this unnatural position of the tongue before allowing it finally to settle back into the mouth. Closure of the jaw then ensued. These patients also exhibited a similar inability to keep the jaw open even when the tongue was not protruded.

FACILITATION OF THE REACTION

The phenomenon of complusive eye opening could be demonstrated independently of compulsive mouth closing and vice versa.

However, if the complexity of the task was increased by having the subject execute simultaneously closure of the eyes, opening of the mouth, and maintaining the tongue protruded, then the patient's resumption of the resting position with the eyes open, the tongue withdrawn, and the mouth closed occurred more readily. Also, when the patient performed any one of these acts and simultaneously attempted to carry out some other simple acts, e.g., pointing to his nose or ear or identifying stimuli used in a sensory examination, then the phenomenon of compulsive eye opening or mouth closure was more readily demonstrated. Emotional reactions, such as laughing or crying, brought on while the patient was attempting to maintain these unusual positions of the eyelids, mouth, and tongue, also led to a return to the resting position.

The position of keeping the eyes closed in the waking state, the mouth open, and/or the tongue protruded is an unnatural one and, for these subjects, a very difficult one. Increasing the complexity of the performance demanded of the patient, either by having him carry out all these three acts simultaneously or by having him participate in motility or sensory examinations, overwhelms the limited capacities of the patient to maintain these positions, and the eyelids and mouth soon return to the more usual positions. Emotional reactions always tend to take over the direction of the motor apparatus. They thereby interfere with the execution of the contrived tests of motility. Brain-damaged subjects, subjected to emotion-arousing stimuli, have great difficulty in holding on to the position which is assumed during the testing procedure.

MENTAL STATUS OF PATIENTS

The phenomenon of inability to sustain the eyes closed or to keep the mouth open and the tongue protruded has been observed in patients with clouding of the sensorium due to uremia, cholemia, increased intracranial pressure, or senile dementia. Under these circumstances it is understandable that the patient would lack the capacity for sustained effort. However, the subjects considered for this report were only those who were well oriented, had preserved memory for recent and remote events, and were able to cooperate well during a comprehensive neurological examination.

The failure to sustain these facial postures is not attributable to impaired memory for these acts or to inattention. Ten of the patients were repeatedly tested. After the first four days of testing the subjects were then urged to carry out the tasks that had been requested on previous days, but the specific instructions were not repeated. Each subject then made correct efforts to carry out the eye closure and other tests, but all exhibited the same compulsive eye opening that they had previously. Several subjects, aware of the examiner's interest, attempted to carry out the tests when they saw the examiner approaching, and again they failed.

Detailed psychological tests were also administered to nine patients in the period when they exhibited these phenomena. All these patients could attend to the tests administered. All subjects performed well in tests of memory and language and showed a capacity for new learning, but showed impairment on tests of visual motor performance and organization. In order to ascertain whether the defects of eye closure and associated movements were related to the inability to carry out other acts requiring sustained effort, other tests were administered which required sustained effort. These tested the ability to count, repeat the alphabet, maintain a grip, hold an extremity extended, tap repeatedly in regular rhythm, execute rapidly alternating movements, and maintain the eyes deviated laterally. All patients were able to carry out each of these tests for 20 seconds or more.

SUBJECTS

Since the first observation, in March, 1953, of these signs, 16 right-handed patients were observed who exhibited these phenomena. They were 15 men and 1 woman, ranging in age from 42 to 75. All patients had hemiplegias. Fifteen had lesions of the

right cerebral hemisphere. Only one had bilateral cerebral lesions, that on the left being more marked. Two patients were found to have right parietotemporal tumors. In 12 others, who had had cerebral vascular lesions, the localization was presumed to be parietal on the basis of sensory defects. Hemianoptic defects were present in 11 patients. Six had shown the syndrome of denial of hemiplegia at the onset of their illness. Hence, 14 patients had presumptive evidence of right parietal lesions. Of the two patients who had intact sensation, one had a right, and one a left, cerebral lesion.

These phenomena were demonstrable in patients whose lesions had occurred two weeks to two years prior to the examination. However, it was also found in four patients with cerebral vascular lesions that they had regained their ability to sustain the eyes closed, the mouth open, and the tongue protruded, in two weeks to one year after the onset of their illness.

OTHER PATIENTS HAVING FOCAL CEREBRAL LESIONS

In the past three months, 25 patients with comparable states of orientation with right hemiplegia due to cerebral vascular lesions, of one day to two years' duration, were examined for these signs. All were capable of performing these acts well. Twelve aphasic patients also failed to exhibit compulsive eye closing.

Seven patients with left hemiplegias have been examined in the same three months who did not show these signs. Three of these subjects had mild to moderately severe left hemiplegias (but without sensory impairment) of one week's to one and one-half years' duration. Three others had severe left hemiplegias and sensory defects of nine months' to five years' duration. Three other subjects with left hemiplegias and sensory defects of one to five years' duration showed minimal evidence of the triad, e.g., minimal opening of the left eye or difficulty in maintaining the tongue protruded.

COMMENT

Although these observations were made independently of any previous reports, a search of the literature revealed that a brief report of this inability to keep the eyes closed was made by Lewandowsky [1] in 1907 in a patient with a left hemiplegia. Despite the compulsive eye opening, the patient's eyes were closed during sleep and closed readily during the attempts to elicit blinking. Zutt,[2] in 1950, reported three more cases, but, of these, one had a rather severe progressive dementia in addition to his left hemiparesis. Each of the two other patients developed left hemiparesis associated with spontaneous subarachnoid bleeding. One of these two had forced grasping (as did one of the patients in this report). The lid-closure phenomenon apparently subsided in both these patients within a few weeks after the onset of the lesion. Schilder [3] referred to this phenomenon also in a patient with encephalitis periaxialis diffusa. The significance of this phenomenon in such diffuse brain disease is difficult to evaluate, since all subjects with pronounced clouding of the sensorium may exhibit an inability to execute motor acts requiring sustained effort. No subjects are included in the present report who were disoriented or had severely impaired memory.

By excluding the patients with profound dementia and combining the observations in these patients with those reported previously,* one is struck by the fact that 18 out of 19 patients had left hemiplegias. The sole exception had bilateral cerebral lesions, but these admittedly were more marked in the left cerebral hemisphere.

This phenomenon has been called an apraxia of lid closure,[1] but the ability of the patients to carry out these acts on command, or even by recalling previous instructions, points against its being truly an apraxia. The designation of this phenomenon as a compulsive eye closure is more appropriate, since the inability to resist the tendency of the eyes to open, despite effort and practice, bespeaks an act which, though initiated as a result of the immediate motivational purposes of the subject, nevertheless escapes his volitional control.

The compulsion to maintain the eyes open during the waking state may be associated

* References 1 and 2.

with the basic alerting and defensive posture of the organism. For example, patients with ptosis make every effort to adjust the position of the head to overcome the potential blindfolding effect of the ptosis. Ataxic subjects tested with their eyes closed readily open their eyes when they sway dangerously, and thereby reveal that they do not rely solely upon a repositioning of their limbs to avoid falling. Finally, most striking are the blind, who, though denied the light, retain the visage of vigilance.

Therein probably lies the explanation of the compulsive eye-opening phenomenon. Early biologically determined patterns of behavior undergo complex modifications by life experiences. Consequently, the behavior of the intact well-motivated subject may be more readily governed by authoritarian direction than by his own elemental drives. However, as a result of brain damage, the experientially acquired controls are weakened, and the behavior, then released from the controls, demonstrates a ready expression of unconditioned behavior patterns. This is illustrated by the emotional and sphincteric incontinence of the severely brain-damaged. Similarly, the severely brain-damaged, not optimally responsive to the examiner's direction, effects a closure of his eyes upon command but soon resumes the pattern appropriate for the general alerting and defensive posture, viz., having his eyes open. This explanation may also account for the phenomenon in the diffusely brain-damaged. But there may also be a special focal emphasis on this function in the right cerebrum, since it is predominantly with right cerebral lesions that this phenomenon is apparent.

SUMMARY

People with diffuse cerebral damage often show a striking inability to keep their eyes closed in the waking state.

However, cooperative, well-oriented patients with good memory, but who have right cerebral lesions, manifest a compulsive opening of the eyes shortly after they have been closed in response to the examiner's command. These patients also have an associated inability to keep the mouth open or the tongue protruded.

It is speculated that this phenomenon represents an inability of the brain-damaged person to maintain a posture opposed to the alerting defensive postural patterns, merely at the request of the examiner. Keeping the eyes open in the waking state is part of the basic vigilance attitude, which the intact subject can overcome on command, but to which the brain-damaged person compulsively reverts.

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Studies on Anxiety Associated with Anticipation of Pain

II. Comparative Effects of Pentobarbital and Morphine

HARRIS E. HILL, Ph.D.
RICHARD E. BELLEVILLE, M.A.
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ABRAHAM WIKLER, M.D., Lexington, Ky.

Traditional thinking and practice favor the belief that the barbiturates are not effective as analgesics. Indeed, Goodman and Gilman [1] have stated that they are likely to induce delirium if given under conditions of pain. Several investigators have mentioned the failure of barbiturates to elevate the pain threshold when measured by the Wolff-Hardy-Goodell technique,[2] and such failure has also been reported when other techniques employing animal subjects were used.* Recently, however, Keats and Beecher have questioned this position in a publication which reports that pentobarbital, although not being as potent as morphine, relieved severe pain in 50% of postoperative patients.

Facilities are not available at this institution for direct clinical studies on the value of barbiturates as analgesics. However, we have approached the problem indirectly on the assumption, previously validated in the case of morphine, that one of the important mechanisms through which drugs exert analgesic action is by reduction of anxiety associated with anticipation of pain.[6] It is hoped that the data presented in this paper may clarify some of the problems involved, particularly in relation to the definition of analgesia, and the factors involved in the relief of pain by the use of drugs.

The method used in this study was based upon the same principles utilized in a previous investigation.[6] This study demonstrated that morphine reduces the disruption of performance which accompanies self-inflicted brief, but painful, electric shock penalties for slow reaction times. It was also shown in a related experiment that this effect was not due to impairment of ability to estimate the intensities of painful stimuli.[7] For the present work only the former technique was employed, with certain modifications designed to improve controls, particularly with reference to motivation. In accordance with the purposes of the investigation, parallel studies were conducted concurrently on different groups of subjects for no-drug, pentobarbital, and morphine conditions.

METHODS AND MATERIALS

Subjects.—Ninety-eight male prisoner patients between the ages of 25 and 50, with histories of narcotic addiction, volunteered for the experiment. Of these, 26 withdrew during the course of the experiments, leaving 72 subjects who completed the procedures.

Apparatus and Procedure.—Although essential features of the previously reported experiment [6] were retained, the instruments and procedure were changed in some respects better to control several variables. Manual reaction times, in milliseconds, were recorded by a modified Dunlap chronoscope when the subject pressed a key in response to the flash of a neon bulb. The apparatus was the same as that employed in the previous investigation except that a Stoelting electronic chronoscope was used for calibrating the Dunlap instrument. The response key and four neon bulbs were mounted in vertical alignment on an opaque screen, ¾, 10, 15, 16, and 17 in. (1.9, 25.5, 38, 40.5, and 43 cm.), respectively, above

From the National Institute of Mental Health, Addiction Research Center, U. S. Public Health Service Hospital.

* References 3 and 4.

a table. For instructional purposes the subject was told that the bulbs would be lit in an "on your mark," "get set," "go" sequence. The lowest light indicated that a trial was beginning. The second bulb from the top flashed two seconds later and indicated that the subject should prepare for a quick response. The other two lights, one slightly above and one slightly below the "get set" bulb, were the stimulus lights. Only one of these was lit for any one trial, the subject responding to either by quickly moving the key to the left. The delay time, or foreperiod, between the warning and the stimulus light was variable, a predetermined random order of 1, 2, and 3 seconds being used.

Stainless steel electrodes covered with saline paste were attached to the reacting hand of the subject for all tests, and, when electric stimuli were used, inductorium-generated shocks of approximately 120 volts and 0.37-second duration were delivered (the shock used in the previous study was approximately 140 volts).

The conditions and number of subjects used on each day are shown in Table 1. On Day 1 no shock was used and control reaction times were obtained on 72 subjects. Twenty-four subjects were employed on each of the three conditions: no-drug, morphine, and pentobarbital (when a drug was used, 15 mg. of morphine sulfate or 250 mg. of pentobarbital was administered intramuscularly 50 minutes before starting the tests).

For the present study, it was necessary that near-minimal reaction times should be obtained on Day 1, because this day's performance set the criterion for later application of shock. This was accomplished by providing a morphine reward (after completion of all experiments), the size of which was made contingent upon "fast" reaction times. These were the conditions of Day 1, *High Motivation*, indicated on Charts 1 and 2. In order to provide adequate practice on this day, four series of 18 reactions each were given at 15-minute intervals.

TABLE 1.—*Mean Reaction Times in Seconds for All Conditions*

Day 1 Practice (High Motivation)			Day 2 Experimental Series (Standard Motivation)						
Group	N		Subgroup	N	(1)	(2)	(3)	(4)	(5)	(6)
No drug	24	0.168	No-shock	12	0.158	0.159	0.160	0.162	0.160	0.160
			with-shock	12	0.184	0.188	0.188	0.212	0.222	0.207
Morphine	24	0.166	No-shock	12	0.179	0.178	0.182	0.176	0.182	0.181
			with-shock	12	0.174	0.168	0.168	0.173	0.169	0.175
Pentobarbital	24	0.158	No-shock	12	0.155	0.154	0.154	0.153	0.156	0.160
			with-shock	12	0.184	0.212	0.216	0.218	0.223	0.220

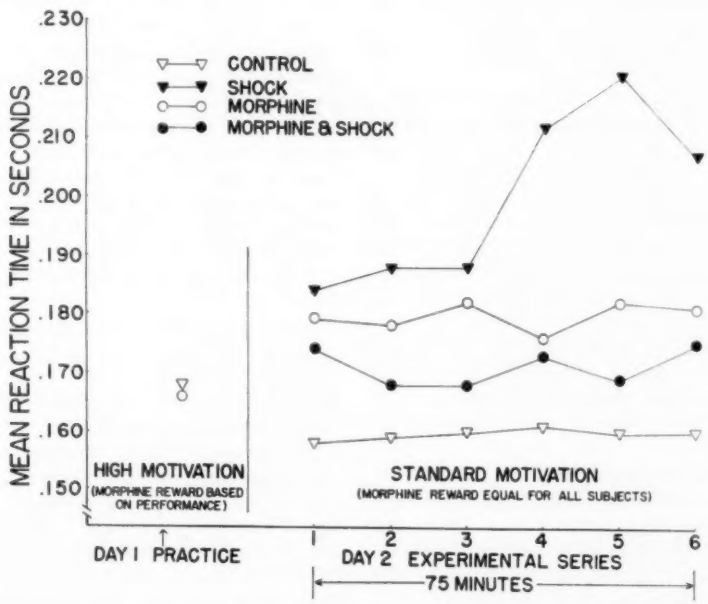

Chart 1.—Mean reaction times showing the effects of morphine under various conditions.

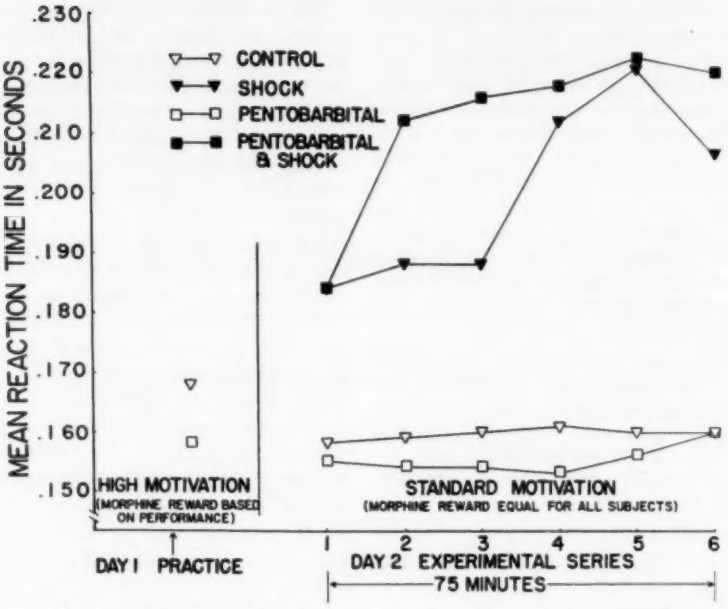

Chart 2.—Mean reaction times showing the effects of pentobarbital under various conditions.

Morphine rewards for Day 2 were equal for all subjects and were not dependent upon efficiency of performance ("Low Motivation"). On this day half of the subjects selected at random from the subjects of each condition (Table 1) received shock for slow reactions, while the other half did not. In this way the three different groups of Day 1 were divided to produce six subgroups, of 12 subjects each, for Day 2: (1) "No-drug, no-shock," (2) "no-drug, with-shock," (3) "morphine, no-shock," (4) "morphine, with-shock," (5) "pentobarbital, no-shock," and (6) "pentobarbital, with-shock" (Table 1). As indicated in the Charts, six series of 18 reactions each were obtained at 15-minute intervals. The subjects in the groups who did not receive shock were told that each series would begin with the second light from the bottom (the "go" signal), and that if their movements were sufficiently quick this light would be used as the signal for all following reactions. Slow reactions, it was explained, would be followed on the next trial by the top light. In this way the subject was given knowledge of his performance and thus might be motivated to increase his speed of reacting. The subjects tested under shock conditions were given the same instructions except that they were told that the flash of the top light would mean that a strong shock would be delivered just as they completed pressing the key. Each subject's Day 1 mean was taken as the criterion for slowness and for applying the upper light for the first series of Day 2. If a subject's reaction time for any particular response was longer than this mean, the upper light was used as the stimulus for the next response and, as indicated above, was followed by shock to the hand. As each series was completed, median reaction times were calculated. If improvement occurred, a new criterion (the lowest median) was established. The criterion was not shifted upward when less efficient behavior began to occur, but was maintained at the lowest point.

Since the subject never knew which of the two lights would appear next and, consequently, never knew when he would be forced to shock himself, the periods between stimulations and between the warning and stimulus lights, under shock conditions, presented an opportunity for the development of anxiety, as demonstrated in the previous study.[6] The subjects maintained that it was not so much the shock that was disturbing, although it was severe, as it was the expectancy or uncertainty of the stimulation.

Treatment of Data.—Since the procedure of Day 1 was utilized chiefly to reduce reaction time and variability, the results on only the fourth series of each condition were used *(Day 1, Practice)*. For these conditions, and those of Day 2, mean reaction times obtained for each subject were combined to give group means for each series. The differences between the means for the various conditions of Day 2 were evaluated by the "*t*" test. Since there is some question as to the validity of this statistic when the distributions of scores are not entirely normal, the *t* values were checked by a nonparametric technique. In view of the previous outcome, a one-sided

distribution of t logically could have been employed for evaluating the differences between "no-drug, no-shock," and "no-drug, with-shock" conditions, and "morphine, with-shock" conditions. This would have effectively doubled the t values. However, since no such logical basis could be employed for treating the differences between "pentobarbital, with-shock" and "no-drug, with-shock" conditions, the two-sided distribution was used for all comparisons.

Only relative comparisons of reaction times can be made between the previous and the present study. The shorter times reported for the present investigation are reflections of changes in motivation and modifications of the apparatus; under certain of our conditions they are as short as, or shorter than, any reported in the literature.

RESULTS

Although the reaction time means for Day 1 are given in Table 1, no statistical evaluation of the differences is presented. For Day 2 the means on "no-drug, no-shock" and "no-drug, with-shock" conditions serve as the basis for the comparisons made in both Charts 1 and 2. Only those comparisons which are pertinent for the development of the present thesis are presented in the Tables. Means for all conditions, however, are shown, and superficial comparisons can be made by inspection of Table 1.

TABLE 2.—*Comparison of Mean Reaction Times, in Seconds, for "With-Shock" and "No-Shock" Under "No-Drug" Conditions*

Series	With-Shock	No-Shock	Difference	σ Mean Difference	t	P
1	0.184	0.158	0.026	0.0121	2.15	<0.05
2	0.188	0.159	0.029	0.0108	2.69	<0.02
3	0.188	0.160	0.028	0.0095	2.95	<0.01
4	0.212	0.162	0.050	0.0228	2.19	<0.03
5	0.222	0.160	0.062	0.0174	3.56	<0.01
6	0.207	0.160	0.047	0.0166	2.83	<0.01

Table 2 and Chart 1 present data on "no-drug, no-shock" and "no-drug, with-shock" conditions. The differences between the means of all six series of the two conditions are statistically significant; in fact, the probabilities of such differences occurring by chance alone are less than 1 in 100 for four of the series, and less than 5 in 100 for the other two series. This outcome is very similar to that of the previous study but is more consistent and more conclusive in showing the disruptive effects of anticipation of painful stimuli on performance. These results are even more impressive when it is considered that it is very difficult consistently to increase the latency of this relatively simple response.

TABLE 3.—*Comparison of Mean Reaction Times, in Seconds, for "With-Shock" Under "No-Drug" and Morphine Conditions*

Series	No-Drug, with-Shock	Morphine, with-Shock	Difference	σ Mean Difference	t	P
1	0.184	0.174	0.010	0.0122	0.82	>0.10
2	0.188	0.168	0.020	0.0072	2.78	<0.02
3	0.188	0.168	0.020	0.0081	2.47	<0.02
4	0.212	0.173	0.039	0.0231	1.69	>0.05
5	0.222	0.169	0.053	0.0179	2.96	<0.01
6	0.207	0.175	0.032	0.0175	1.83	<0.07

After administration of morphine, shock penalties did not result in a significant increase in reaction time. Although the "morphine, with-shock" curve is slightly higher at all points than the "no-drug, no-shock" curve, none of the differences reached statistical significance, and, furthermore, under morphine conditions the shock motivation actually shortened reaction times. Comparison of the "morphine, with-shock" curve with that of the "no-drug, with-shock" shows that the latter is higher at all points, and, as Table 3 shows, the differences in three of the series on these conditions are significant beyond the 0.02% level. Thus, morphine prevented the occurrence of the disruption so evident in "no-drug, with-shock" conditions. The improved controls of the present study are reflected in the consistency of obtained results, including a terminal performance (Series 6) on "morphine, with-shock,"

TABLE 4.—*Comparison of Mean Reaction Times, in Seconds, for "With-Shock" Under "No-Drug" and Pentobarbital Conditions*

Series	No-Drug, with-Shock	Pentobarbital, with-Shock	Difference	σ Mean Difference	t	P
1	0.184	0.184	0.000	0.0162	0.00	>0.10
2	0.188	0.212	0.024	0.0282	0.85	>0.10
3	0.188	0.216	0.028	0.0296	0.95	>0.10
4	0.212	0.218	0.006	0.0311	0.19	>0.10
5	0.222	0.223	0.001	0.0278	0.04	>0.10
6	0.207	0.220	0.013	0.0258	0.50	>0.10

which does not show the lengthened mean reaction time found on the previous study.

The effects of 250 mg. of pentobarbital under two conditions is shown in Table 4 and Chart 2. Under the standard motivation of Day 2, following the high motivation of Day 1, "pentobarbital, without shock" resulted in the shortest mean reaction times obtained on the experiment. This result is in marked contrast to those recorded under shock conditions. The means of all six series are significantly greater than the "no-drug, no-shock" means. The "pentobarbital, with-shock" curve is also higher at all points, except for the first series, than is the "no-drug, with-shock" curve, although none of these differences are statistically significant. Thus, pentobarbital did not prevent the disruptive effects on this performance, which is associated with anticipation of pain and actually may have enhanced such effects.

COMMENT

The major purpose of this study was to determine whether barbiturates exert actions similar to those of morphine on anxiety associated with anticipation of pain, anxiety being defined operationally in terms of increased visuomanual reaction times under conditions of repeated self-penalization for poor performance. Inspection of Charts 1 and 2 provides an unequivocal answer. After morphine, repeated shock penalties shortened reaction times, in contrast to the marked slowing effects of such painful stimuli under non-drug conditions. These results are in complete accord with those of the previous study on other subjects.[6] On the other hand, barbiturates, even in doses which produced mild intoxication (250 mg.), did not alter the effects of repeated self-penalization on reaction time (Table 4, Chart 2).† Actually, the performance of the subjects was poorer, although the differences between the "no-drug, with-shock" and the "pentobarbital, with-shock" condition were not statistically significant. It may therefore be concluded that anxiety associated with severe experimental pain is not reduced by pentobarbital.

As mentioned previously in this paper, data are accumulating which indicate that reduction of anxiety associated with anticipation of pain is a necessary action of a potent analgesic. The results are conclusive to date only with respect to morphine. Therefore, although work on other analgesics and non-analgesics is now in progress at this laboratory, it can only be stated with assurance at the present time that if reduction of such anxiety is a necessary action of a potent analgesic, pentobarbital should not be included in this class of drugs.

Analgesia may be defined in different ways, depending upon the therapeutic purposes of the physician. In certain situations pain relief with concomitant hypnotic effects may be desirable. In other situations, a slighter degree of pain relief with a quieting effect may be sufficient, as with the addict patient who reports that he is not substantially relieved of pain. Frequently, however, the desired result is a verbal affirmation of pain relief, without concomitant production of excessive drowsiness, neuromuscular weakness and incoordination, etc.

Irrespective of whether analgesia is defined in terms of the observer's estimate or the patient's verbal report, the data of Keats and Beecher [5] on the effects of administration of 60 and 90 mg. of pentobarbital intravenously on severe postoperative pain indicate that this drug is not a potent analgesic. Analysis of their results shows that the reported figure of 50% "pain relieving rate" is derived from data based on the experimenter's estimate of the degree of "comfort" achieved, rather than on the verbal report

† Of incidental interest for the present study, but of considerable significance in other contexts, are the effects of morphine and pentobarbital on simple visuomanual reaction times when rewards are based upon performance (Charts 1 and 2, *Day 1*). It will be noted that these drugs either had no effect or actually shortened (accelerated) reaction times in this particular experimental situation. As will be shown in a later paper, this does not occur when morphine and pentobarbital are administered in experimental situations that are the same in all respects except that rewards are independent of performance.

of the patient.‡ Furthermore, if one employs only the data obtained when pentobarbital was administered as the first drug or after saline, the incidence of "comfort" achieved falls to 38.8%. When only verbal report is used as the criterion, computation reveals that analgesia was accomplished in only 26.8% of the patients.[10] This would appear to be only a small increase over the effectiveness of the placebo employed.

Thus, pentobarbital, when used clinically, is not a potent analgesic, and it does not relieve severe experimental anxiety. Nevertheless, for discovering a possible relationship between anxiety reduction and analgesia, it may be important to demonstrate, on the one hand, whether the barbiturates are effective in relieving mild clinical pain and, on the other hand, whether they reduce mild experimental anxiety. If barbiturates are effective in mild clinical pain and reduce anxiety associated with mild experimental pain, the relative analgesic actions of morphine and pentobarbital would appear to be dependent upon the same mechanism. However, if barbiturates are mild analgesics but do not reduce mild anxiety, the pertinent mechanisms of action of these drugs would appear to be different.

‡ A careful examination of the Keats and Beecher report indicates that they use two criteria of analgesia: "comfort" and "pain relief"; the former is based on the observer's estimate, the latter on the patient's verbal report. It would appear as though both these indices might be employed as measures of analgesia. However, "+ comfort," which is the criterion for calculations presented in Table 1,[5] departs from Dr. Beecher's earlier statements that analgesia should be defined in terms of the degree of pain relief as reported by the subject. If percentage calculations are based on the number of patients reporting relief (b + d, Table 1),[5] the conclusions regarding the effectiveness of pentobarbital are quite different from those presented. The best estimate of the action of pentobarbital would appear to be given by obtaining the mean of Groups I, II, and III, in which pentobarbital was given either as the first drug or after saline. Estimated in this way, pentobarbital produced pain relief, as judged by the patient, in 26.8% of the cases, and comfort, as judged by the observer, in 38.8%.

A definitive solution of the clinical problem could be reached by means of such studies as those of Houde[10] and Keats and Beecher.[5] For experimental investigation of mild anxiety, the procedure used in the present study would have to be modified considerably, since reaction time is not greatly altered by mild electric shock. Studies are currently in progress which may aid in further clarifying some of these problems concerned with analgesia.

SUMMARY

In 72 subjects who were former drug addicts, repeated self-penalization for slow visuomanual reaction times produced a striking disruption of performance, which was manifested by marked increase in the latency of the responses (slowing of reaction time).

Following administration of morphine (15 mg. i. m.) such disruption was greatly reduced, and, furthermore, morphine prevented any significant effect of such shock penalties upon reaction times.

In contrast, administration of pentobarbital (250 mg. i. m.) failed to reduce the disruption of performance which accompanies painful self-penalization; indeed, pentobarbital appeared to enhance the effects of shock penalties, although the increase was not statistically significant.

It is concluded that, whereas morphine, as previously demonstrated, acts in a powerful manner to relieve anxiety associated with the anticipation of severe pain, this attribute is not shared by pentobarbital. The significance of these findings is discussed with reference to the problems of analgesia.

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Accidental Russian Spring-Summer Viral Encephalitis

Cases Occurring in Two Laboratory Workers, One Fatal, with Postmortem Study

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Russian spring-summer virus encephalitis has been recognized in man in parts of the European and Far Eastern U. S. S. R. and in a few countries of Eastern Europe. Its viral agent is very closely related to, and possibly identical with, that of louping ill of sheep, long recognized in Scotland. Nonfatal infections in laboratory workers with the virus of louping ill have occasionally occurred.* Both viruses are known to be transmitted in nature only by ticks. Naturally acquired Russian spring-summer virus infections usually occur in forest workers bitten by ticks that have acquired their infection from small rodents. Although small rodents are the mammalian hosts, the tick is considered the true reservoir, inasmuch as the virus can be passed congenitally through the egg.

Only three cases of the human disease due to the Russian virus have been recorded outside of Russian and Asian areas. Two were nonfatal laboratory infections diagnosed serologically, one by Olitsky and the other by Smadel (Sulkin and Pike [4]); no details were provided. The third was a fatal laboratory infection reported by Jervis and Higgins [5] from upper New York State. It was suspected that the infection was contracted through contamination with animal excreta. The patient was a woman aged 45. The course of the illness was stormy, with death occurring on the fourth day after onset. A virus identical with the Russian encephalitis virus was recovered from the central nervous system (CNS).

Our report concerns one fatal infection and one inapparent infection with Russian encephalitis virus occurring simultaneously in 1951. Although the source and mechanism of infection was not known when the patient became ill, subsequent study and reconstruction of the sequence of events lead us to believe that the infections were simultaneously acquired in the following manner.

Two persons, a man aged 28—the principal subject of this report—and a woman aged 32, were working at opposite ends of a laboratory bench about 12 ft. long in a closed laboratory 10×16 ft. in size with a 12-ft. ceiling. The man had completed extracting with benzene a powdered brain suspension of mice infected with Russian spring-summer virus. The brain substance, still damp with benzene, was in the Gooch filter in which the extraction had been made, and the filter had been covered with the lid of a Petri dish and placed in a sealed glass desiccator jar. The petcock on the top of the desiccator had been connected by a rubber hose to a water-aspirator-type pump. Under this vacuum the brain suspension had become powder-dry. Our subject turned off the water aspirator and left the room for 10 to 15 minutes. On returning, instead of closing the petcock on the top of the desiccator before removing the hose, he pulled the hose off abruptly, at a distance of probably less than 12 in. below his nose and mouth. A plainly audible "pop" was heard by both persons, indicating that considerable vacuum remained when the hose was removed. Simultaneously the Petri dish cover flew

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* References 1 to 3.

off the filter. Later it was noted that powdered material formerly in the filter now was spread over much of the inner surface of the desiccator.

Those in the room contended that nothing could have been expelled into the air because there had been a vacuum in the desiccator, but it is our belief that a resurge probably discharged some of the fine powder into the air almost directly into the operator's face. The powder had probably been highly diluted in the air when eventually encountered by the other worker. Since this incident was not reported until after the onset of illness, poliomyelitis, Japanese B encephalitis, and Russian virus, all of which had been handled by this worker, were considered in an effort to establish an etiological diagnosis. Not until one worker had died and the serological tests had been completed on both persons could the agent be definitely determined. These observations lent support to the events as reconstructed.

CLINICAL HISTORY

The patient, a man aged 28, had been working for about two years in one of the virus laboratories of the Department of Epidemiology and Microbiology of the Graduate School of Public Health of the University of Pittsburgh. He had been vaccinated against some of the arthropod-borne encephalitis viruses, including those of the Western equine and Japanese B forms in 1950 (third injection of Japanese B in October, 1950), but not to the Russion spring-summer variety. Aside from occasional "colds," he had had no recognized virus infections during the previous few years. In the autumn of 1950 he had had an attack of headache centering over the right eye, which lasted a few days, an attack similar to that which heralded the onset of his fatal illness.

Present Illness.—The onset of the present illness (Nov. 1, 1951) was marked by fever and by headache localized to the frontal region above the right eye. At home his condition grew worse. On the third day he became confused and then somnolent.

On admission to the hospital, on Nov. 4, he was somewhat somnolent and disoriented. There was questionable weakness of the left arm. The tongue deviated to the left, and the left cheek and side of the mouth sagged. Stiffness of the neck was noted. The pupils responded well to light and in accommodation. The fundi could not be examined. The deep reflexes were hypoactive, and a Babinski reaction was elicited on the left. The temperature was 105.2 F, and during the next two days it ranged between 103.8 and 105.6 F; then for about two days it fluctuated between 101 and 103.4 F, and during the last few days it leveled off at about 100 F. The pulse rate gradually increased to 140; but after tracheotomy it fell with the temperature to about 110, and for the rest of his illness it remained between 100 and 110. The respiration rate increased with the temperature and pulse up to 72 per minute until after tracheotomy, when it ranged between 30 and 50 (Fig. 1). The blood pressure fluctuated considerably.

Soon after admission the patient became comatose. Conspicuous twitching of the muscles of the right side of the face was noted. By the second day there was pharyngeal and palatal paralysis. By then the paralysis of the limbs, which was flaccid in nature, had spread to involve the muscles of the left side of the face and neck, the left arm, the left leg, and possibly the intercostal muscles of the left side. On the next day the intercostal muscular weakness was more conspicuous, and the left diaphragm was partially involved. Pulmonary atelectasis developed. Tracheotomy was performed on Nov. 7. Improvement had occurred by Nov. 10, with the intercostal muscles of the left chest beginning to function, but there was continuing difficulty in aspirating the thick mucus from the bronchi.

From time to time the patient vomited "coffee-ground" material. Incontinence of urine and feces persisted. After the first few days the patient became restless and had vigorous involuntary movements of the right arm and leg. Later, all such movements gave way to flaccidity. Death occurred on Nov. 13, approximately 13 days after onset of the illness.

Throughout his illness, the patient received energetic chemotherapeutic and antibiotic medication, including sulfadiazine, penicillin, oxytetracycline (Terramycin), and streptomycin. He was also given intravenous nutritional therapy, such as protein hydrolysate (Amigen) and glucose. On the day of admission, after the first blood specimen had been withdrawn, and after skin sensitivity to rabbit serum was found to be negative, he was given 10 ml. of a Japanese B hyperimmune rabbit serum.

Laboratory Data.—Repeated uninalyses showed a normal specific gravity, a trace of albumin, and occasional finely granular casts. The hemoglobin and the erythrocyte counts were normal. Blood leucocytes were 21,000 per cubic millimeter, with 94% neutrophiles on admission; they then ranged between 11,800 and 14,650, always with a relative neutrocytosis. The blood nonprotein nitrogen was within normal limits. The blood sugar was slightly elevated, being from 120 to 135 mg. per 100 cc., but these values were obtained after the administration of glucose intravenously. The CO_2-combining power of the blood fluctuated between 50 and 68 vol.%. The plasma chlorides were usually low, between 370 and 400 mg. per 100 cc. The total serum protein was 6.9 gm., albumin 4.9 gm., and globulin 2.0 gm., per 100 cc., giving an A/G ratio of 2.6. Culture of blood removed on Nov. 4 was negative.

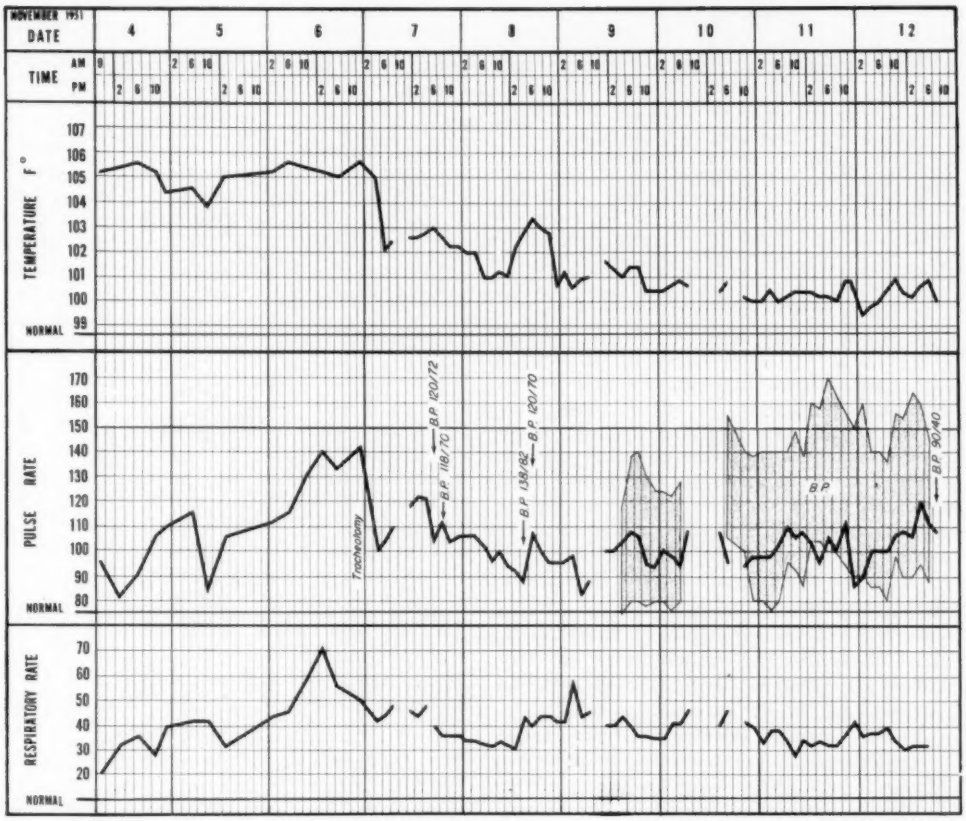


Fig. 1.—Temperature, pulse rate, respiration, and blood pressure during the course of the illness.

The spinal fluid pressure on admission was 31 cm. of water. The sugar totaled 105 mg. and the protein 56 mg., per 100 cc. There were 281 white cells per cubic millimeter; a differential cell count was not made. No growth appeared in cultures. On Nov. 17 the spinal fluid pressure was recorded again at 31 cm. of water; the protein, at 800 mg. per 100 cc. This time there were 700 red blood cells and 34 white cells, of which 90% were lymphocytes. Considerable difficulty had been encountered in entering the spinal canal, probably accounting for the red blood cells.

MATERIALS AND METHODS

Autopsy was begun two hours after death.† Blood was withdrawn from the heart under sterile conditions for use in serological tests.

†Dr. Paul Gross, Pathologist of St. Joseph's Hospital, Pittsburgh, performed the autopsy and made available the various materials on which this paper is based.

The brain was removed from the skull as aseptically as possible, whereupon various parts were taken for attempted isolation of virus. These consisted of the medial one-half of the lower midbrain, part of the thalamus, and the medial one-half of the pons and medulla oblongata. On removal of the spinal cord, blocks from representative levels were also taken for virus studies.

Upon fixation of the brain and spinal cord in 10% formalin, blocks were removed from all representative CNS levels and from every gyrus bilaterally. Some blocks from the CNS were embedded in celloidin and others in paraffin. As a preliminary measure, sections from the paraffin blocks were stained by hematoxylin and eosin and then examined with a view to determining the nature and scope of the pathological process. Sections from celloidin-embedded blocks were stained by cresylecht violet, by the hematoxylin-Van Gieson method, and by the Weil and Lillie methods for myelin. Paraffin sections were used for impregnation of axis cylinders by the Bodian[1] activated-strong silver protein (Protargol) method.

TABLE 1.—*Serological Tests in a Case of Fatal Laboratory Infection with Russian Spring-Summer Encephalitis Virus*

Date of Specimen	Time Relation to Onset	Russian S.-S. Neut. Index Ip.*	Russian S.-S. Neut. Index Ic.*	Russian S.-S. C. F.†	Jap. B Neut. Index Ip.	Jap. B Neut. Index Ic.	Jap. B C. F.
6/27/50	17 mo. before	—10	.....	0	1	....	0
11/ 4/51	3 days after	20,000	.....	0	16	....	0
11/ 9/51	8 days after	>160,000	.....	0	6,300‡	....	0
11/13/51	(Autopsy) 12 days after	>160,000	3,000	8	<30	....	0

* Ip. indicates intraperitoneal mouse test; Ic., intracerebral mouse test.
† Reciprocal of serum dilution. 0 indicates no fixation at 1:4 dilution.
‡ Ten cubic centimeters of Japanese B hyperimmune rabbit serum was administered on Nov. 4, 1951, just after blood sample of that day was taken.

Other standard stains employed included oil red O. Through the courtesy of Dr. Moises Polak (Buenos Aires) and of Dr. W. J. H. Nauta (Washington, D. C.), frozen sections were impregnated by Hortega methods for glia and by a modified Bielschowsky method for axis cylinders, respectively. The cranial nerves and spinal roots were stained by hematoxylin and eosin and oil red O and by the Masson trichrome and Bodian activated-strong silver protein methods.

The degree of leptomeningeal involvement in the various blocks from the cerebral cortex was indicated on brain charts in terms of 1+ to 4+, and from these a composite drawing was made (Fig. 2). Visual impression was also relied on in charting the lesions and their topography in the CNS (Fig. 4).

VIRUS ISOLATION ATTEMPTS AND SEROLOGICAL STUDIES

In an attempt to isolate a virus of the arthropod-borne encephalitis group, blood serum and spinal fluid of Nov. 4 were each injected into groups of six mice 3 to 4 weeks of age and six suckling mice about 5 days old. Mice of both ages were given the undiluted material both intracerebrally and intraperitoneally. No virus was isolated.

In an attempt to isolate poliomyelitis virus, feces of Nov. 9 were prepared as a 10% suspension. After clarification by centrifugation at 2,000 and 16,000 rpm, the supernatant was sedimented in a Spinco Ultracentrifuge for two hours at 30,000 rpm. The pellet was resuspended in 11 ml. of diluent containing a suitable antibiotic mixture and injected into the thalamus of two rhesus monkeys. No illness occurred in these animals.

Several blocks of the CNS obtained at autopsy were repeatedly tested in mice for encephalitis viruses as separate and pooled tissue in 10% suspension and in serial 10-fold dilution up to 1:100 dilution of the original suspension. Both adult and suckling mice were used, as described in the tests with serum and spinal fluid. No viral agent was isolated.

Serological tests were performed by two methods, neutralization and complement fixation. Since adult mice are highly susceptible to the Russian virus when they are inoculated in any peripheral or visceral region—and thus become highly sensitive test animals for antibody response—the intraperitoneal, rather than the intracerebral, method was used in all but one test with that virus. The same method was employed with respect to the Japanese B virus, but in this instance suckling mice were necessarily used. The detailed techniques

TABLE 2.—*Serological Tests on Subclinical Infection with Russian Spring-Summer Encephalitis Virus*

Date of Specimen	Time Relation to Exposure	Russian S.-S. Neut. Index Ip.*	Russian S.-S. Neut. Index Ic.*	Russian S.-S. C. F.†	Jap. B Neut. Index Ip.*	Jap. B Neut. Index Ic.*	Jap. B C. F.†	St. Louis Neut. Index Ip.*	St. Louis Neut. Index Ic.*	St. Louis C. F.†
10/26/50	1 yr. before	8	.....	0	>100,000‡	.....	0	..	1	0
11/21/51	34 days after	700	320	0	>10,000	.....	8	..	..	..
12/ 5/51	48 days after	50,000	2,000	8	.....	.....	4	..	..	0
12/21/51	64 days after	>700,000	6,300	4	.....	3,000	0	<10	..	4
2/14/52	119 days after	.....	.....	0	.....	13,000	0	<10	..	4
3/17/52	151 days after	.....	.....	0	.....	.....	0	..	..	0

* Ip. indicates intraperitoneal mouse test; Ic, intracerebral mouse test.
† Reciprocal of serum dilution. 0 indicates no fixation at 1:4 dilution.
‡ This subject had been vaccinated repeatedly and "exposed" in the laboratory to Japanese B virus over a long period of time.

of the neutralization tests employed have been described elsewhere.[6] Complement fixation was performed with benzene-extracted mouse-brain antigens,[7] using the tube method. The results of these tests on one specimen of serum taken over a year before infection and at intervals after onset of the illness are presented in Table 1. It will be noted that no detectable antibody to the Russian virus was present in 1950, that on the day of hospitalization (Nov. 4) the neutralization index was already 20,000, and that on Nov. 9, and also at the time of autopsy, the index had risen above 160,000. Complement-fixing antibody first became detectable in the serum taken at autopsy, on the 12th day after the onset of illness. The studies for Japanese B virus antibody revealed no antibody of significance on Nov. 4. The index of 16 might represent a small residual from previous vaccination. Antibody was found five days after the Japanese B immune serum was administered, but this had essentially disappeared by Nov. 13. No complement-fixing antibodies to Japanese B virus were detected.

The evidence for Russian virus infection becomes even stronger when the results of tests on sera from the other worker who was simultaneously exposed are examined. Table 2 presents the results of tests to the Russian, the Japanese, and the related St. Louis virus on a series of specimens taken from 1 year before this exposure to 151 days after. This worker showed an increase to Russian virus-neutralizing antibodies by both the intraperitoneal and the intracerebral method and an increase, and then disappearance, of complement-fixing antibodies. She had Japanese B antibodies from previous vaccinations and/or laboratory exposures, but never had detectable St. Louis neutralizing antibodies. The early complement-fixing antibody response to Japanese B virus and the somewhat later one to the St. Louis virus are probably cross reactions due to a related antigen and cannot be considered specific, since they were not accompanied by a rise in neutralizing antibodies.

GROSS AUTOPSY

Thoracic and Abdominal Viscera.—The only significant alteration observed on opening the thoracic cavity was partial collapse of both lungs. The heart weighed 370 gm. and showed no changes. The left lung weighed 450 gm. and the right 600 gm. The entire left lung and the lower part of the right were of a rubbery consistency entirely devoid of crepitancy, and when these parts of the lungs were placed in water, they sank to the bottom of the receptacle. On section, the cut surfaces of the lower parts of the right lung were dark and red and slightly retracted, and contained numerous poorly defined, darker-red, finely granular nodulations, averaging 5 mm. in diameter. Less conspicuous nodulations of the same kind were found in the left lung and the upper part of the right lung. Tenacious mucoid material was found in the tracheobronchial tree. The tracheobronchial lymph nodes were soft and edematous.

The liver weighed 1670 gm. and appeared normal. No changes were observed in the gall bladder or biliary passages. The spleen weighed 300 gm. The follicles were not visible, and the pulp could not be scraped free. The kidneys weighed 430 gm. and appeared in the realm of normal. Adrenals, pancreas, and prostate showed no changes. The only abnormality observed in the gastrointestinal tract was a small amount of "coffee-ground" material in the stomach.

Brain and Spinal Cord.‡—The dura appeared normal. The brain, which weighed 1530 gm., was moderately swollen, as judged by the narrowness of the sulci and fissures, the flattening of the gyri, and the presence of a slight tentorial pressure cone. The leptomeninges were clouded, particularly along the course of the large blood vessels of the lateral cerebral tissue and convex surface of the cerebrum and in the region of the median fissure in front of the optic chiasm. Capillary engorgement was evident over most of the convex surface. On removal of blocks from the brain, no parenchymal change was visible. The ventricles did not appear dilated. No alteration was detected in the spinal cord.

MICROSCOPIC OBSERVATION

Thoracic and Abdominal Viscera.—The changes in the lungs consisted of atelectasis, edema, and lobular pneumonia. The only other structure affected was the prostate gland. Here, there was rather pronounced leucocytic infiltration of the acini. The periacinar stroma was somewhat edematous and contained a scattering of leucocytes.

CENTRAL NERVOUS SYSTEM

Leptomeninges.—In many regions of the cerebral hemispheres the subarachnoid space was widely distended, and in some places the leptomeninges were ballooned. Cell accumulations were found in all sections, their greatest concentration being in the region of the lateral cerebral fissure (Fig. 2). They were both perivenous and diffuse. The majority of the cells were mononuclear, ranging from small lymphocyte-like cells to obvious macrophages (Fig. 3*A* and *B*). Many of the small cells were regarded as reactive histiocytes in various stages of development, a view supported by the observation that they still clung to their parent arachnoid trabeculae by means of a wide base of cytoplasm. Rows of cells of the lymphocyte series were occasionally encountered in the pia, and now and then they were continuous into the Virchow-Robin

‡ Armed Forces Institute of Pathology Accession No. 518138.

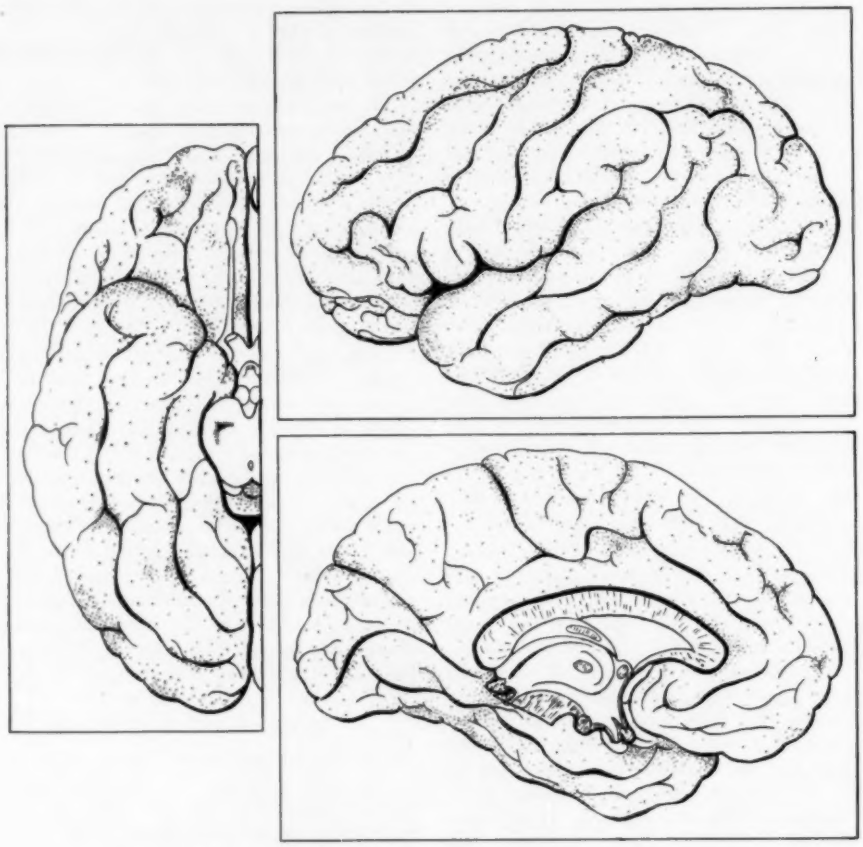


Fig. 2.—Topographical distribution of the meningitis.

spaces of vessels penetrating the cortex. There were scattered focal proliferative changes of the arachnoid membrane. Small extravasations of erythrocytes were seen here and there in the arachnoid meshes.

Brain.—The topographical distribution of the lesions is to be seen in Figure 4.

Cerebral Cortex: The cerebral cortex was relatively spared. The subpial cortical lamina and the part of the cortex at the depths of some sulci and fissures, particularly the calcarine, were slightly spongy. Blood vessels in the cortex were usually free from change. No intimal proliferation was observed. In most of the sections an occasional vessel was surrounded by a few mononuclear cells. The incidence can be gathered from Figure 4. Tiny hemorrhages, usually perivascular, were seen in an occasional section.

Nerve cells here and there in most of the sections exhibited retrogressive changes, consisting mainly of shrinkage of the cell body, increased basophilia of cytoplasm and nucleus, and sometimes corkscrew deformation of apical dendrites. Scattered nerve cells were judged to have undergone irreversible changes. Such changes predominated in the upper three or four laminae, and occasionally were most conspicuous perivascularly. Sections prepared by a Hortega method showed condensation of neurofibrillae in some nerve cells. In oil red O preparations abundant fat was found in the cytoplasm of virtually all nerve cells.

In an occasional section there was activation and slight proliferation of subpial astrocytes. Also, a fair number of proliferated oligodendrocytes and rod cells were visible perivascularly or were scattered at random. Small neuronophagic nodules were occasionally noted. The most conspicuous changes were in the lower two or three laminae of the island of Reil; they consisted of neuronophagic nodules, diffusely scattered proliferated neuroglial and rod cells, vessels surrounded by a few mononuclear cells, and occasionally neuronophagia. The glial and mononuclear cell response lessened rather abruptly where the cortex bordered the extreme capsule; it became rather prominent again when

the claustrum came into range, and it was altogether absent in the external capsule, though in the latter there were perivascular cuffs of lymphocytes bordering the claustrum. What has been said applies to the more rostral part of the island of Reil, at the level of the head of the caudate nucleus. More caudally, at the level of the anterior perforated substance, the island of Reil was considerably less affected.

Sections from three of the blocks from the precentral gyrus showed only a few perivascular mononuclear cells. In a fourth, from the region adjacent to the lateral fissure, there was a rather heavy accumulation of cells in the leptomeninges, a somewhat greater number of perivascular cells in the cortex and white matter than elsewhere, and somewhat more red cells than usual. Only one tiny, but clear-cut, neuronophagic nodule was found in the several sections from this region. Sections from the parietal lobe impregnated by the Nauta modification of the Bielschowsky method displayed advanced degenerative changes in axis cylinders in lower laminae, judged, from their position, to be thalamocortical fibers (Fig. 5*A*). The subcallosal gyrus and the parolfactory area were relatively spared.

Hippocampal Formation: The dentate gyrus and the major part of the pyramidal layer (including Sommer's sector) were intact. At caudal levels the hilar parenchyma was spongy, and its nerve cells showed slight to moderate disintegrative changes, suggesting early necrosis. Occasional neuronophagic nodules were encountered, and rather numerous proliferated oligodendrocytes and rod cells and a few astrocytes were strewn diffusely in the damaged area. The adjacent alveus and the fimbria of the hippocampus appeared normal.

Cerebral White Matter: The white matter of the corona radiata exhibited mild perivascular sponginess, a few petechiae—about as many as in the cortex, but somewhat larger—and scattered sparse perivascular collections of mononuclear cells, mostly macrophages. Mononuclear cell nodules, usually minute and oftenest immediately subcortical, were sometimes observed (Fig. 5*B*). There were also a few areas in which pleomorphic cells were strewn in the white matter; a fair number of the cells were proliferated astrocytes, and others resembled activated Hortega microgliocytes; also, the endothelial cells of some capillaries appeared swollen (Fig. 5*C*). A few of these diffuse cell accumulations were found in the corpus callosum, which

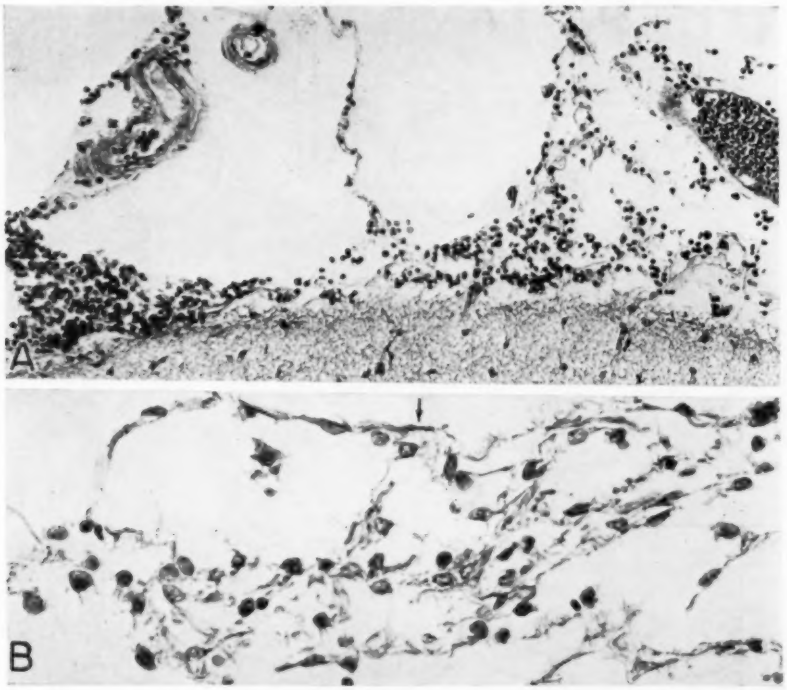


Fig. 3.—*A*, leptomeninges, showing collections of cells of the lymphocyte series and histiocytes. A. F. I. P. Acc. No. 52-100-518138. *B*, arachnoidal membrane (arrow) and trabeculae, showing proliferated histiocytes. A. F. I. P. Acc. No. 52-98-518138.

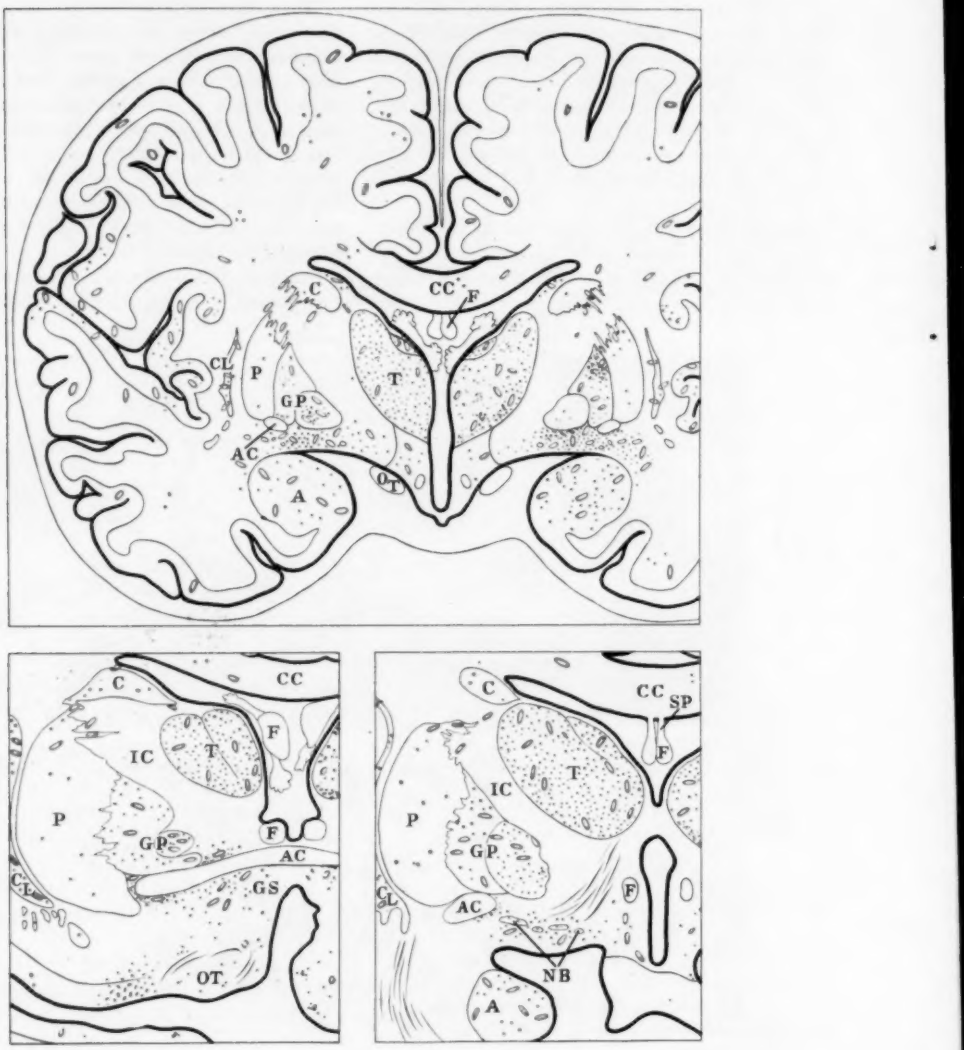


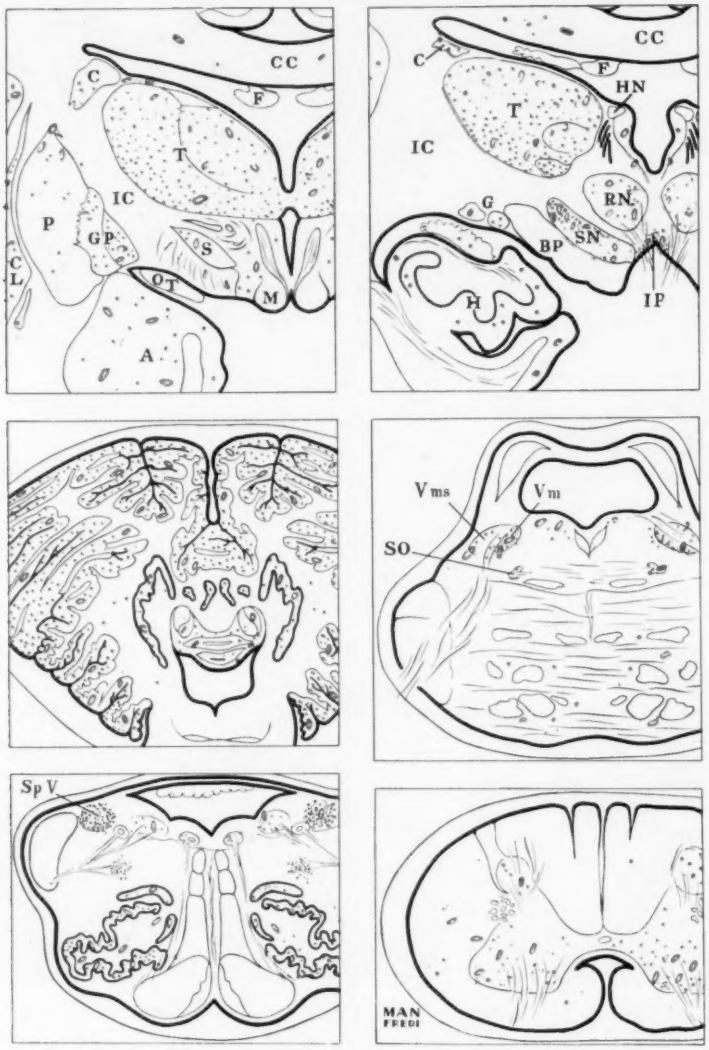
Fig. 4.—Left, topographical distribution of lesions in the cerebrum. The ovals represent perivascular collections of cells, and the dots, the parenchymal lesions, i. e., infiltrations of hematogenous and/or adventitial cells into the parenchyma and locally reactive glial cells.

Right, topographical distribution of lesions in the brain stem, cerebellum, and spinal cord.

otherwise was normal except for suggestive patchy proliferation of the oligodendroglia. The internal capsule seemed unaffected.

Caudate Nucleus and Putamen: These were among the structures least affected. There was patchy proliferation of oligodendroglia cells and of occasional astrocytes, especially in the cell bridges between caudate nucleus and putamen. The few mononuclear cell nodules present were exceedingly small. Perivascular lymphocyte collections were also few and far between, but were fairly abundant in the white matter bordering the caudate nucleus and putamen.

Globus Pallidus, Anterior Perforated Substance, Amygdala, and Adjacent Structures: The lateral segment of the right globus pallidus was found permeated by oligodendroglia. Microglia-like cells and astrocytes were also seen, but were in smaller numbers. Many nerve cells were absent. Only a few of the perivascular spaces were occupied by hematogenous cells, mainly lymphocytes. The background structure of the globus pallidus was retained



except for one moderate-sized reactive-cell-packed area, in which it was softened. Oil red O revealed only a few fat-containing cells, and these were perivascular. The medial segment of the globus pallidus was characterized by moderate cell loss and a sprinkling of microglia-like cells. On the left side the lateral segment of the globus pallidus was less affected, and the medial segment more so. In sections impregnated by the von Braunmühl silver method only a few of the myriad nerve fibers were irregularly swollen or in a state of disintegration. The anterior commissure appeared normal.

The anterior perforated substance was severely affected. On the right side its dorsal half had undergone partial softening, with replacement of the parenchyma by a variety of cells, including oligodendrocytes, astrocytes, and gitter cells, and some persisting degenerating nerve cells were being phagocytosed (Fig. 6*A*). Within this area the capillaries were dilated, and the walls and Virchow-Robin spaces of most of the venules contained numerous inflammatory cells. Tiny hemorrhages were also seen here and there. Only a few cells comprising the nucleus basalis were intact. Sections stained by the Holzer method for glial fibers were negative. The ventral half of the anterior perforated substance was relatively spared, and the degree of damage and number of inflammatory and glia cells lessened as one passed ventrolaterally into the amygdala and medially into the lateral hypothalamic region. On the left side the corresponding part of the anterior perforated substance was less

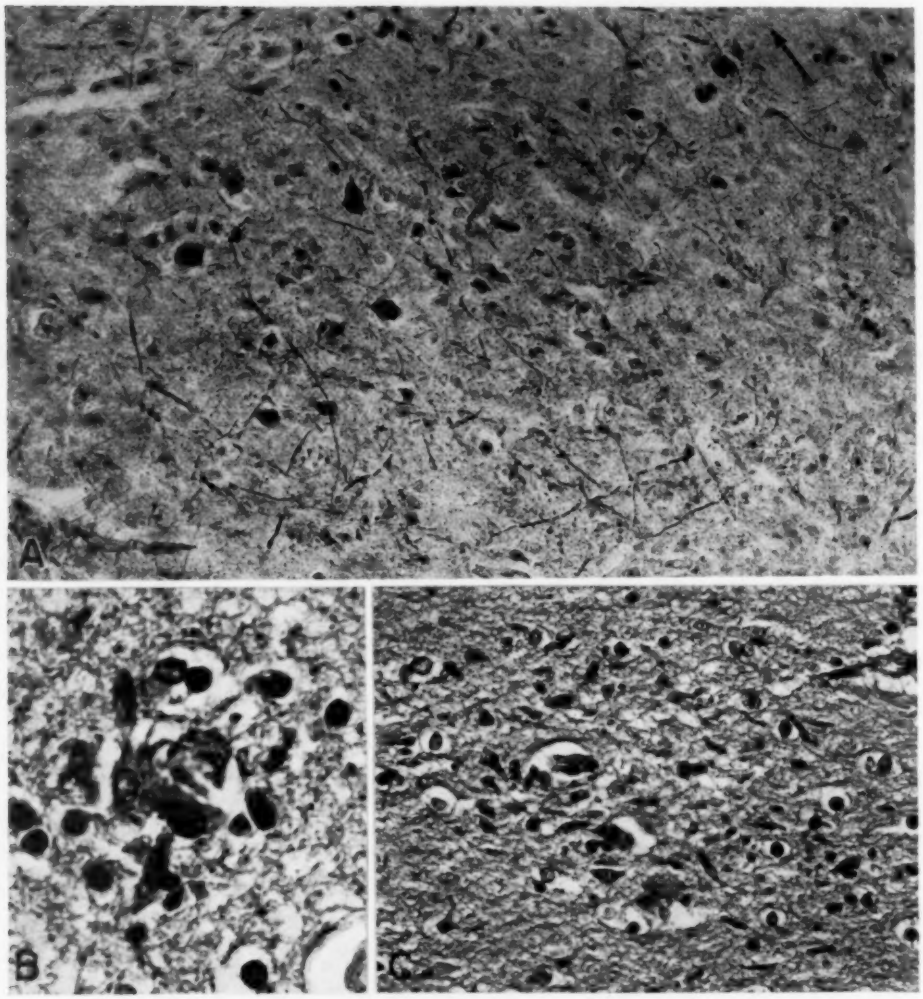


Fig. 5.—*A*, lower cortical laminae of parietal cortex, showing degenerating axis cylinders. The arrow points toward the meninges. Bielschowsky-Nauta silver impregnation. A. F. I. P. Acc. No. 54-19207-518138. *B*, cell nodule in cerebral white matter. A. F. I. P. Acc. No. 52-99-518138. *C*, rather ill-defined spongy focus in the subcortical white matter, showing scattered microgliocytes and neurogliocytes. A. F. I. P. Acc. No. 52-91-518138.

affected, but numerous small focal areas of partial softening were noted along the borders of the anterior commissure. Closely adjacent to the anterior perforated substance the cerebral cortex was riddled with cell nodules and many nerve cells were being phagocytosed (Fig. 5*B*).

In the right amygdala there was hardly a low-power field that could be considered normal. Most conspicuous was a series of neuronophagic nodules, in the midst of which the nerve cells were undergoing phagocytosis. These were in the central region of the amygdala, but here, as elsewhere in the amygdala, there were microglia-like cells and spherical mononuclear cells either diffusely scattered or congregated into more or less compact groups. Oligodendrocytes and astrocytes had also increased considerably in number. Where the parenchyma was most overrun by these cells, the nerve cells displayed necrosis without phagocytosis, and vessels were surrounded by lymphocytes. Phlebitis also was encountered. Involvement of the left amygdala was of the same nature but considerably less pronounced.

Diencephalic Structures: Thalamic involvement varied from section to section, but in general was severe. At any given level numerous nerve

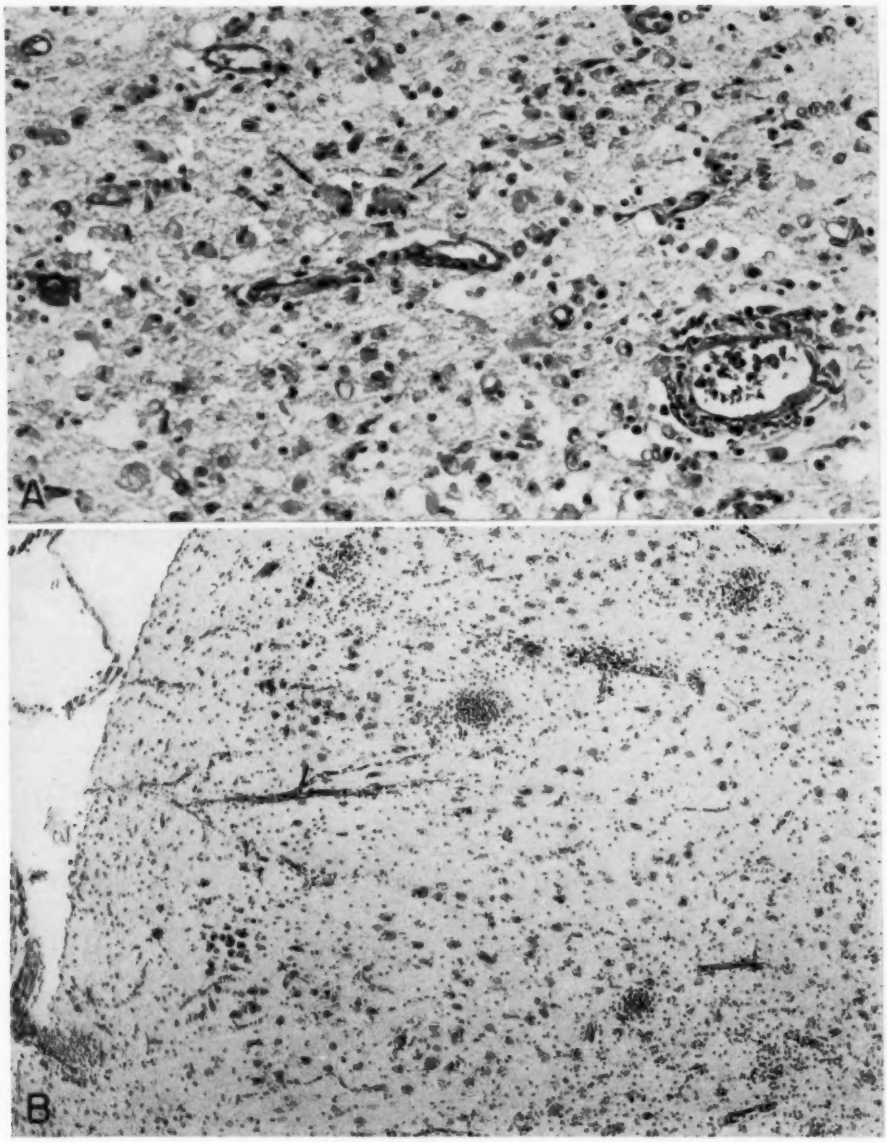


Fig. 6.—*A*, anterior perforated substance, showing occasional nerve cells which are being phagocytosed (arrows) and a variety of reactive elements. Cresylecht violet stain. A. F. I. P. Acc. No. 518138-17. *B*, cortex adjacent to anterior perforated substance, showing many infiltrative cells, some in the form of large nodules. Numerous perivascular cells are also visible. Hematoxylin-Van Gieson stain. A. F. I. P. Acc. No. 518138-53-10092.

cells were in a state of necrosis (Fig. 7*A*) or were absent. Perivascular collections of mononuclear cells were fairly common (Fig. 7*A*). Oligodendrocytes were clearly in excess in perivascular zones of tissue breakdown (Fig. 7*B* and *C*), and in such areas coagulated edema fluid could frequently be demonstrated. Throughout much of the thalamus there was a patternless array of proliferated oligodendrocytes intermixed with a few hypertrophic astrocytes. Sections impregnated by a Hortega method confirmed the presence of myriad proliferated oligodendrocytes and occasional astrocytes. Advanced axonal degenerative changes were observed in sections impregnated by the

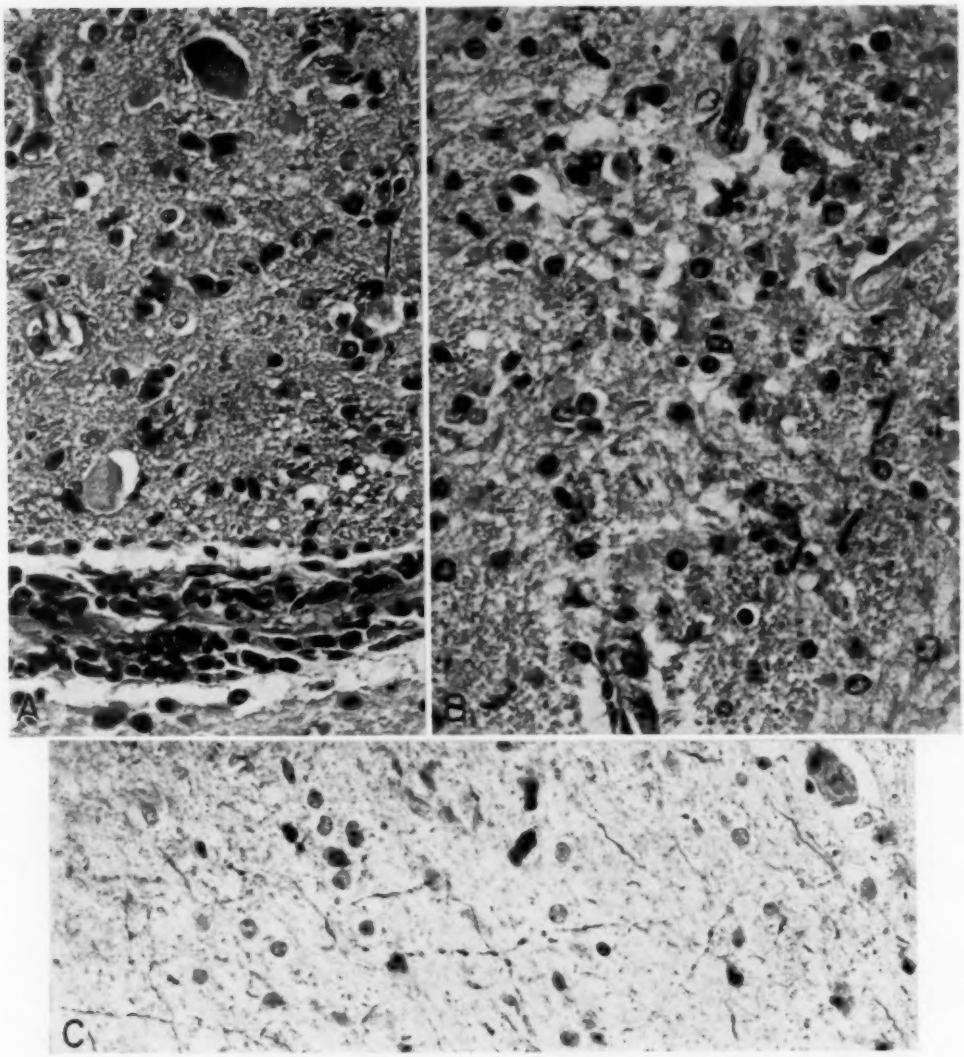


Fig. 7.—Thalamus. *A*, cells of the lymphocyte series occurring perivascularly; necrotic nerve cell bodies, one of which is being phagocytosed (arrow), and numerous proliferated macrogliocytes. A. F. I. P. Acc. No. 518138-123. *B*, perivascular breakdown of tissue with reactive glia. A. F. I. P. Acc. No. 518138-125. *C*, increase in oligodendrocytes and astrocytes, with disintegration of axis cylinders. Bielschowsky-Nauta silver impregnation. A.F. I. P. Acc. No. 518138-122.

Bielschowsky-Nauta method (Fig. 7*C*). In some regions not visibly related to vessels there were congregations of proliferated and invasive cells, with microglia-like cells constituting a more or less conspicuous component.

The hypothalamus was but little affected. At the level of the infundibulum bilaterally a few vessels of the lateral hypothalamic area were surrounded by lymphocytes and other mononuclear cells, and the parenchyma displayed a diffuse increase in oligodendroglia and a scattering of enlarged astrocytes. Dorsally in this area occasional nerve cells were in the process of being phagocytosed by mononuclear cells. The only other hypothalamic nucleus affected was the posterior. Here, a few nerve cells were disintegrated or necrotic; the blood vessels were engorged with blood; tiny hemorrhages had occurred, and there was evidence of rather severe edema. The fornix and mammillothalamic tract were unaffected.

The habenular nucleus showed nothing of consequence, nor was any change noticed in the habenulo-

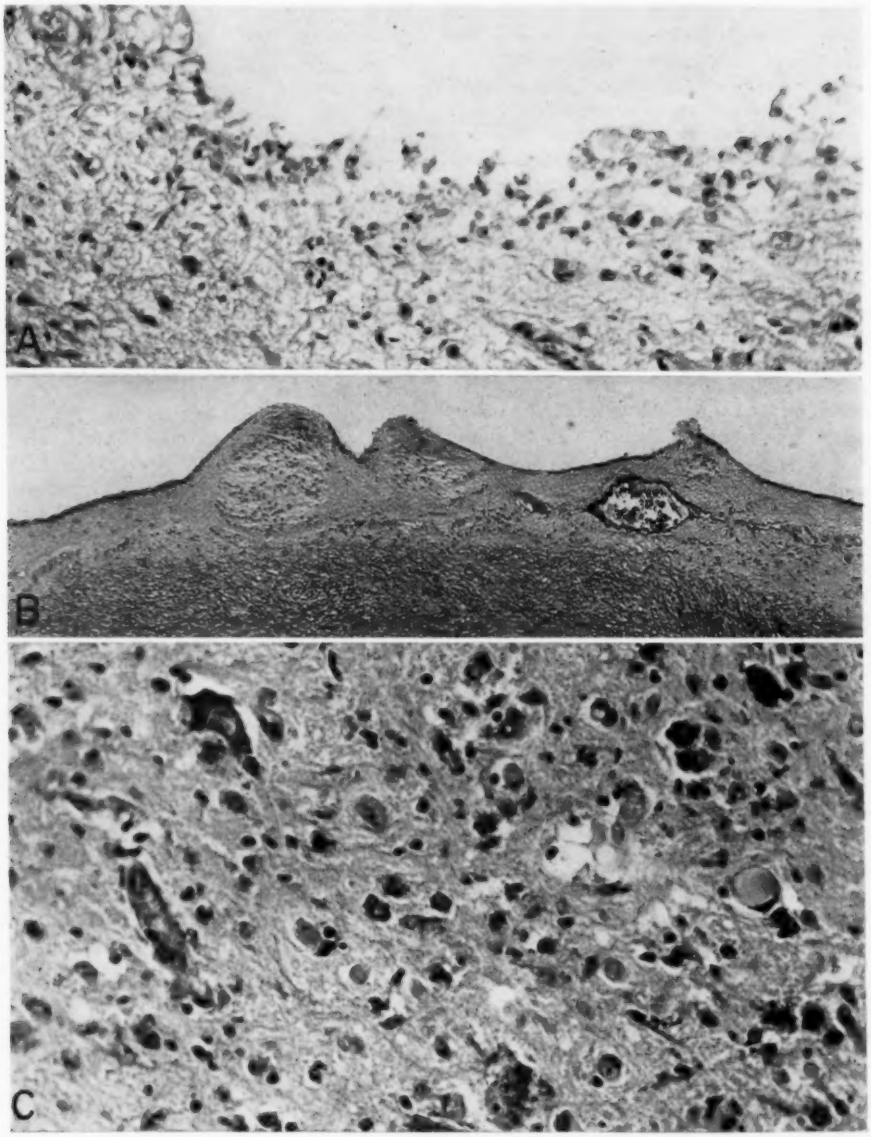


Fig. 8.—*A*, proliferative changes in the wall of the third ventricle. The floor of the third ventricle is to the left. A. F. I. P. Acc. No. 518138-52-186. *B*, ependymal granulations in region of interventricular foramen. A. F. I. P. Acc. No. 53-10128. *C*, pars compacta of the substantia nigra. A. F. I. P. Acc. No. 518138-102. Very few nerve cells remain. Pigment of destroyed cells has been ingested by macrophages.

interpeduncular tract; also, the pineal body appeared unaffected, although the subarachnoid space around it contained many macrophages. The subthalamus bilaterally was characterized by a mild generalized increase in oligodendrocytes and astrocytes and a congregation of a few lymphocytes in perivascular spaces. Occasional nerve cells of the subthalamic nucleus and zona incerta were amorphous, and some seemed to have disappeared. The same was true for the geniculate bodies.

Ventricular Walls and Choroid Plexuses: The ependymal epithelium and subependymal cell matrix were in most regions intact. In the lowermost part of the third ventricle, adjacent to the tuberoin-

fundibular nucleus and surmounting the infundibulum, there was slight proliferation of the ependymal epithelium and the subependymal matrix (Fig. 8*A*). Somewhat more active ependymal proliferation was encountered at the premammillary level. The walls of the lateral ventricles, particularly in the region of the interventricular foramen and head of the caudate nucleus, were characterized by scattered, prominent bulbous granulations (Fig. 8*B*). A few granulations of subependymal origin were noticed also in the wall of the fourth ventricle at the pontile level.

Deeper in the subependymal cell matrix, especially adjacent to the head of the caudate nucleus, a moderate number of the vessels were surrounded by lymphocytes, together with a few plasma cells. Otherwise, no change was encountered. The septum pellucidum was free from change.

The choroid plexuses were of normal appearance except for an occasional minute aggregate of mononuclears in the connective tissue core of the plexus near the hippocampal formation.

Midbrain: The brunt of the attack on the midbrain was borne by the substantia nigra, and here the pars compacta suffered considerably more than the pars diffusa (or reticulata). The involvement of the pars compacta was rather patchy, the lateral cell groups being most affected. Nerve cells had disappeared, phagocytosis of others was in progress, and many macrophages had ingested melanin pigment; moreover, astrocytes and oligodendrocytes were on the increase (Fig. 8*C*). Cells of the lymphocyte series were to be seen in the perivascular spaces of most of the small vessels; some were in the immediately adjacent parenchyma, suggesting that they reached that region by breaking through the membrana limitans gliae. The pars diffusa was architecturally intact, though a fair number of its nerve cells showed retrogressive changes. It contained a scattering of rather spherical mononuclear cells with distinct cytoplasmic borders and increased numbers of oligodendrocytes and astrocytes. These changes in the pars diffusa were more clear-cut at the superior collicular than at the inferior collicular level. It is estimated that at least 60% of nerve cells of the substantia nigra had disappeared.

The histological picture of the red nucleus was approximately the same as that of pars diffusa of the substantia nigra. The motor tegmentopeduncular nucleus (situated just dorsal to the substantia nigra) contained excess oligodendrocytes and a few necrotic cells. Much the same picture was true of the colliculi. The periaqueductal gray matter was spared except for a few sizable collections of lymphocytes around an occasional laterally situated vessel. The dorsal tegmental nucleus appeared normal. The aqueduct was of normal size, and its lining ependymal cells were unaltered. The basis pedunculi was free from change.

The nuclei of the oculomotor nerve were significantly affected. These nuclei were occupied by pleomorphic mononuclear cells, and there were the inevitable scattered neuronophagic nodules. A few nerve cells had disappeared, and the indigenous glia, especially the oligodendroglia, had proliferated. Perivascular inflammatory cells were inconspicuous. The most evident damage was in the ventrolateral and dorsolateral components of the nucleus. Many of the cells of the Edinger-Westphal nucleus had undergone retrogressive changes. The nucleus of the mesencephalic tract of the trigeminal nerve was spared.

The interpeduncular nucleus at the inferior collicular level stood out because of the severity of its involvement. Invasive cells had overrun the nucleus; glia had proliferated; a fair number of the cell bodies still visible were in the process of being phagocytosed, and the number of lymphocytes in perivascular spaces exceeded those seen elsewhere in affected parts of the brain.

The tegmental nuclei, the parabigeminal body, and the nuclei and fibrae pontis at the inferior collicular level were all virtually free from change.

Pons: Only one lateral half of the pons was available for study. The pars basilaris pontis appeared normal except for occasional neuronophagic nodules and perivascular mononuclear cells. In the superficial part of the floor of the fourth ventricle, and rarely in the tegmentum, a few vessels were surrounded by lymphocytes, with the concentration greatest in the region of the nucleus caeruleus. In this nucleus a few invasive pleomorphic mononuclear cells were noted. Close inspection of the medial part of the floor of the fourth ventricle revealed retrogressive changes in nerve cells, patchy increase of oligodendroglia, a neuronophagic nodule or two, and hypertrophic changes in the endothelial cells of blood vessels. The same was true of the superior central tegmental nucleus, though here a conspicuous number of nerve cells had been transformed into spherical pink-staining amorphous bodies (in hematoxylin-eosin preparations), suggesting necrosis, and near such cell bodies there was an inconspicuous, although indubitable, increase in oligodendrocytes. The brachium conjunctivum and brachium pontis were free from change.

At a level of the pons where the motor and main sensory trigeminal nuclei come into greatest prominence, the pars basilaris pontis was intact except for an occasional rather small cell nodule in the nuclei pontis. Of all nerve cell aggregates at this level, only the motor trigeminal nucleus had been severely attacked. Relatively few of its nerve cells remained, and the nucleus as a whole was pervaded by glia and by foreign mononuclear cells. In the

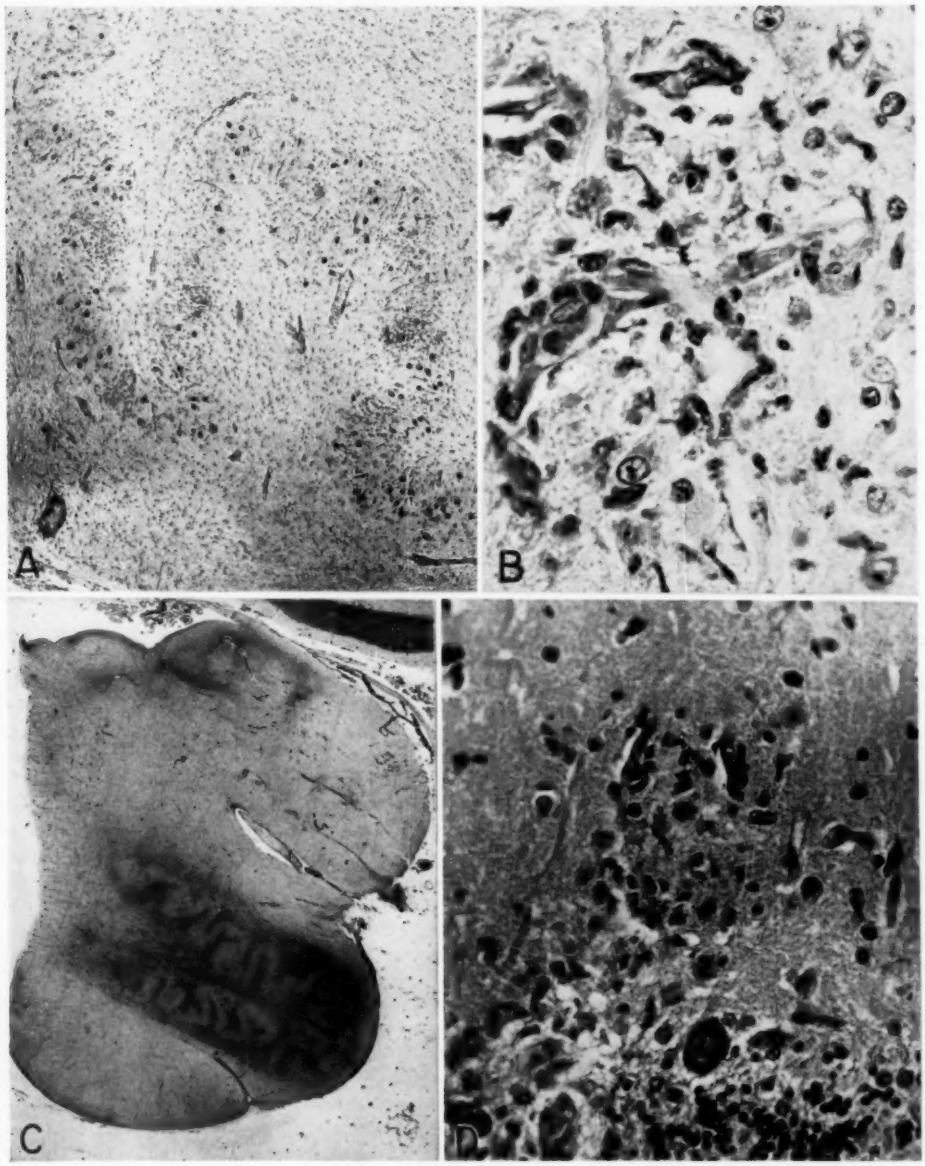


Fig. 9.—*A*, inferior olivary nucleus, showing several large neuronophagic nodules. A. F. I. P. Acc. No. 54-2823-518138. *B*, same nucleus, showing the cellular components of a nodule. A. F. I. P. Acc. No. 53-10120-518138. The pleomorphic mononuclears present perivascularly are regarded as hematogenous or adventitial in origin. The parenchymal cells are astrocytes, invasive mononuclear cells, microgliocytes, and oligodendrogliocytes. *C*, medulla oblongata, with astrogliosis of the inferior olivary, medial vestibular, and other nuclei. Holzer crystal violet stain. A. F. I. P. Acc. No. 54-19210-518138. *D*, cerebellum, showing a relatively small cell nodule emanating from the region from which a Purkinje cell has disappeared. A. F. I. P. Acc. No. 53-10119-158138. *A*, *B*, and *D*, Cresylecht violet stain.

main sensory trigeminal nucleus the reactive process was almost as pronounced, but the nerve cells had not suffered much reduction in number, although they were all strikingly pyknotic. The superior olivary nucleus was slightly affected, and the superior central tegmental nucleus apparently not at all. Again, brachium pontis and brachium conjunctivum were intact.

At a lowermost level of the pons there were a few disintegrated, presumably necrotic, nerve cells in various nuclei, with obvious proliferation of astrocytes only in the medial vestibular nucleus. The nuclei of the abducent and facial nerves were among the cell aggregates unaffected.

Medulla Oblongata: Only one lateral half of this part of the brain stem was available for the study. At all levels the inferior olivary nucleus and the accessory olivary nuclei were strikingly changed. Focal areas of these structures were occupied by cell nodules (Fig. 9*A*). Between some of the nodules there were nerve-cell-poor areas containing diffuse glial and presumably invasive mononuclear cells, as in the right lower corner of the inferior olivary nucleus in Figure 9*A*. In the region of cell nodules, regressive changes had taken place in myelin sheaths and axis cylinders. At low magnification no alteration in the myelin picture was visible. In cell nodules in an early stage of evolution neuronophagia was obviously still in progress. Perivascular mononuclear cell collections were rather few. In the example illustrated in Figure 9*B* there are pleomorphic mononuclear cells in the perivascular space, a bizarre assortment of mononuclear cells in the parenchyma, presumed to be mostly histogenous or hematogenous, and cells with large clear nuclei which are astrocytes. A few of the smaller cells may be oligodendrocytes.

Diffuse gliosis was present in the region of the inferior olivary nucleus, as revealed by the Holzer method (Fig. 9*C*). Within the nucleus the glial fibers were rather sparse, but they were numerous in the hilus and along the periphery of the nucleus. The processes of the proliferated astrocytes in the inferior olivary nucleus did not take the Holzer stain. Moreover, the gliosis in the region of cell nodules was no richer than elsewhere. The conclusion reached was that the matting of glial fibers was normal, as was known to Weigert [8] many years ago.

As to the reticular formation, there was none of the circumscribed pallor seen in some cases of bulbar poliomyelitis. Some of the nerve cells identified as belonging to the nucleus ambiguus were swollen and otherwise distorted, and the number of oligodendrocytes and astrocytes was increased. The same was true for the nucleus solitarius, lateral vestibular nucleus, hypoglossal nucleus, dorsal nucleus of the vagus, and the spinal trigeminal nucleus. On the other hand, the medial vestibular nucleus showed severe cell loss. The Holzer stain was positive in the region of most of the nuclei mentioned (Fig. 9*C*), but, as in the inferior olivary nucleus, the gliosis was out of proportion to the nerve cell loss and none of the processes of the astrocytes within the nuclei were Holzer-positive.

At the lowermost bulbar levels the nuclei gracilis et cuneatus were of normal appearance, but in the corresponding tracts occasional perivascular cuffs of lymphocytes were to be seen.

Cerebellum and Its Meninges: The leptomeninges of the cerebellum were somewhat more severely affected than those covering the cerebral hemispheres. Here and there the subarachnoid space was strikingly ballooned, as a result, presumably, of rupture of trabeculae. Perivascular collections of cells of the lymphocyte series were numerous, as were also activated histiocytes. Both types of cells were commonly seen extending down into the molecular layer in perivenous spaces. Oil red O revealed occasional fat-filled macrophages in the arachnoidal meshes.

The cerebellum had been heavily attacked. In the cerebellar cortex a common picture was that of cell aggregates emanating from the regions from which Purkinje cells had disappeared (Fig. 9*D*). Such aggregates extended into the molecular layer as a wide or narrow column and often reached the pial surface of the folium. The Virchow-Robin spaces of vessels within or adjacent to cell aggregates frequently contained lymphocytes and other mononuclear cells: As a rule, the greater the number of cells in the parenchymal aggregates, the more numerous were the perivascular mononuclear cells. Not infrequently a linear group of these cells extended through the breadth of the molecular layer, and in such instances could be seen adjacent to disintegrating Purkinje cell dendrites. The farther the mononuclear cells were from the Purkinje cell bodies or from cortical vessels, the greater was their tendency to be pleomorphic; some outlying cells had the configuration of Hortega microglial cells. Sections impregnated by an Hortega silver method failed to show clear-cut evidence of proliferated Hortega microglia cells among the cell aggregates. In Sudan-stained sections a few of the cell nodules contained rather numerous fat-laden cells, which had moderate-sized, centrally placed, spherical nuclei and rather delicate branching processes, conspicuous because of the fat globules they contained.

An attempt was made to determine the topography of the mononuclear cell nodules in the cerebellar cortex. This was done by the simple device of placing an ink mark next to each nodule and then examining the slide with the unaided eye. Sections from all cerebellar levels were covered indiscriminantly with ink marks. No part of the cerebellar cortex seemed appreciably less affected than any other.

The dentate nucleus bore a close resemblance to the inferior olivary nucleus as far as type of lesion was concerned—and we refer here to the nerve-cell destruction and encompassing aggregates of mononuclear cells in the parenchyma and peri-

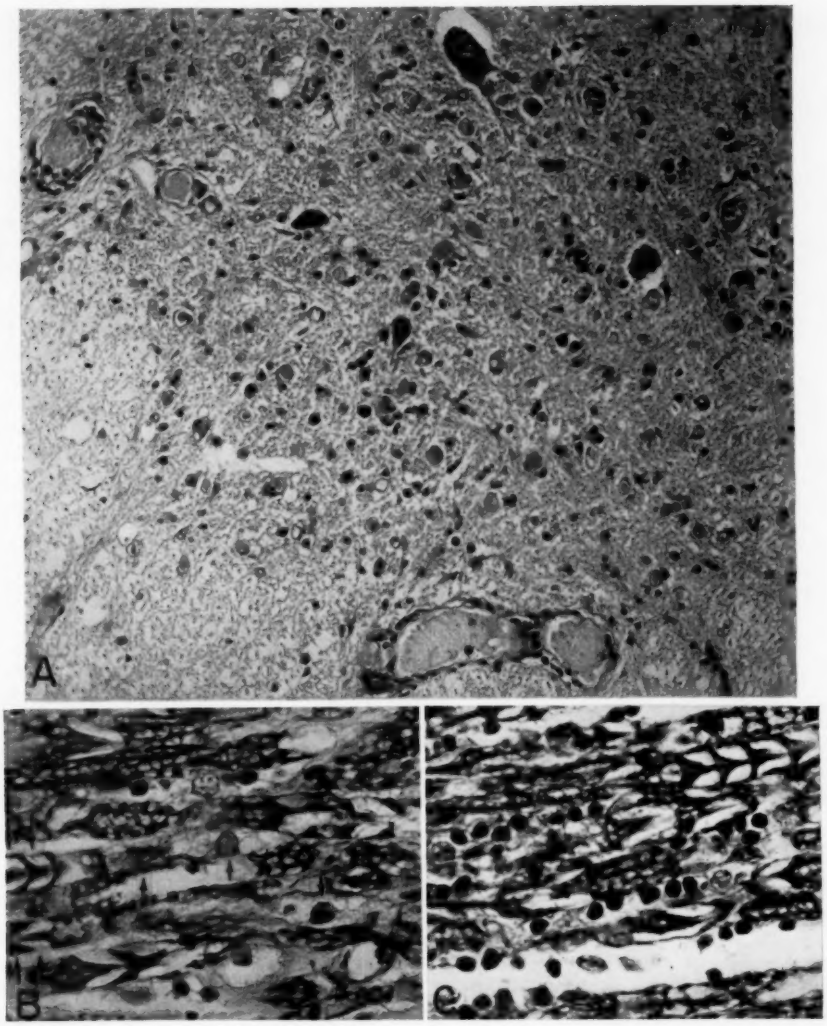


Fig. 10.—*A*, anterior horn of spinal cord. The majority of the nerve cells have been replaced by neuroglia. A few cells of the lymphocyte series are present perivascularly. Cresylecht violet stain. A. F. I. P. Acc. No. 53-10125-518138. *B*, oculomotor nerve, illustrating nerve fibers from which myelin sheath and axis cylinder have disappeared and in which the Schwann tubule now contains macrophages (single arrows). Intact segments of the corresponding nerve fibers are visible (double arrows). A. F. I. P. Acc. No. 54-19902-518138. *C*, same nerve in which rows of macrophages occupy otherwise empty Schwann tubules. A few histogenous or hematogenous cells are also to be seen in the endoneurium. A. F. I. P. Acc. No. 54-19901-158138. *B* and *C*, Masson trichrome stain.

vascularly. The degree of involvement was, however, less than in the inferior olivary nucleus. The same was true of the nuclei fastigii et emboliformis. The nucleus globosus had been converted into a pool of gitter cells. The Holzer stain was virtually negative.

The white matter of the cerebellum was spared except for a few lymphocytes around occasional vessels.

Spinal Cord.—Only the cervical and thoracic segments of the cord were available for study. There was a certain monotony in the pathological picture (Fig. 10*A*). At any given level most of the anterior horn cells had disappeared. Only an occasional one had normal features. Astrocytes and oligodendrocytes had taken over the territory of the anterior horns, and capillaries were more prominent than usual. Larger vessels had a sclerotic

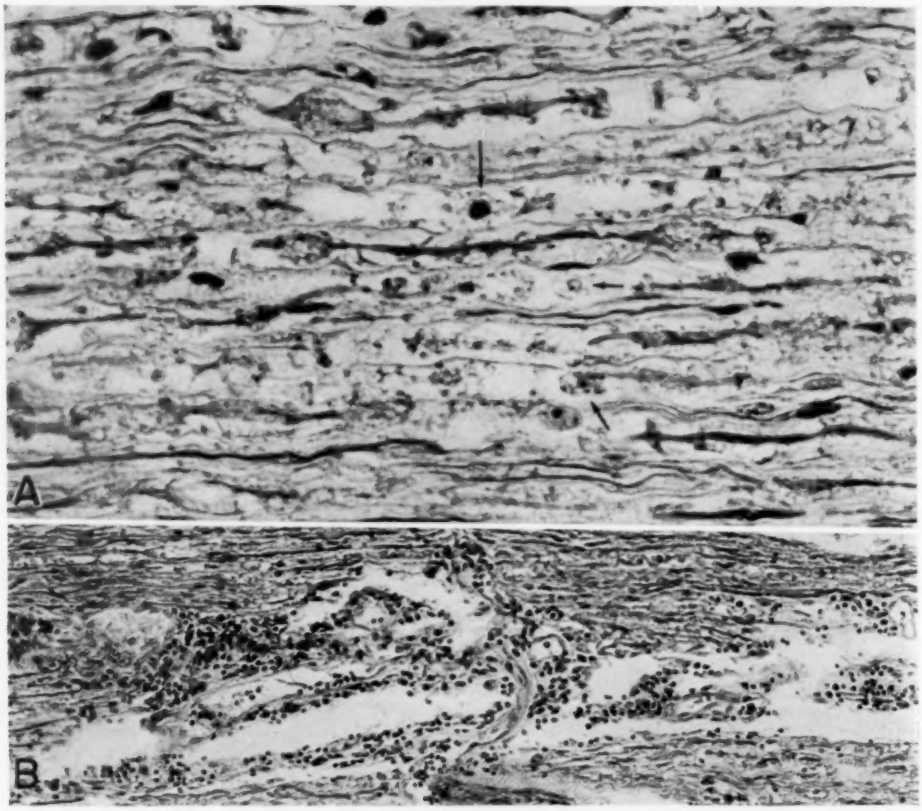


Fig. 11.—Anterior spinal root. *A*, macrophages (arrows) in Schwann tubules in which axis cylinders are degenerated or from which they have disappeared. A. F. I. P. Acc. No. 52-95-518138. *B*, perivascular collections of lymphocytes and other mononuclear cells in the endoneurium. A. F. I. P. Acc. No. 52-93-158138. Bodian activated-silver protein (Protargol) method.

appearance. An occasional vessel was surrounded by numerous cells of the lymphocyte series. In short, the inflammatory process had a "burned-out" appearance. A few nerve cells in the posterior horns had disappeared, and reactive glia and perivascular lymphocytes were sparse. The column of Clarke was unaffected. The white matter was normal except for a rare perivascular collection of lymphocytes. Very few inflammatory cells were found in the leptomeninges.

Peripheral Nervous System

Cranial Nerves.—The olfactory nerves and the optic nerves, chiasm, and tracts appeared normal. As to the other cranial nerves, only short segments attached to the brain were available for study. The leptomeninges surrounding an occasional nerve (e. g., the right fourth) contained scattered or dense accumulations of lymphocytes and other mononuclear cells, especially perivascularly.

The nerve changes varied in kind and degree depending on the nerve examined. In some nerves, particularly the third, fourth, and seventh, there were rather numerous fibers in which myelin and axis cylinders had degenerated and in which Schwann cells had proliferated. Such changes, which included "balling" of myelin, were regarded as evidence of Wallerian degeneration. Scattered perineurial vessels were surrounded by pleomorphic mononuclear cells, and here and there short rows of small mononuclears of the lymphocyte series had extended into the adjacent endoneurium. A few vessels were conspicuous because of enlargement of their endothelial cells. No thrombi were observed. Some lesions in motor nerves were suggestive of periaxial segmental neuritis of the Gombault[9]-Stransky[10] type, but axis cylinders of the corresponding parts of the neural segments had disappeared (Fig. 10*B*). The presence of rows of macrophagic elements in Schwann tubules (Fig. 10*C*) was taken as evidence of Wallerian degeneration. Sections stained by oil red O showed fat globules in the cytoplasm of only an occasional macrophage.

The motor root of the fifth nerve was implicated, whereas the sensory root was free from change.

Because of the history of terminal bulbar palsy, especial attention was given the vagus nerves. The majority of the rootlets appeared normal. In the remainder, scattered myelinated fibers showed degenerative changes of the Wallerian type, and there were small collections of mononuclear cells perivascularly. No clear-cut changes were detected in nonmyelinated (autonomic) fibers.

Examination of the glial part of the cranial nerves revealed no changes except for a few short rows of mononuclear cells, adjacent to which occasional distortion or disrupted axis cylinders could be found.

Spinal Nerve Roots.—Only cervical and thoracic spinal nerve roots were available for study. A slight to moderate number of mononuclear cells were found in the leptomeninges around the roots, and sometimes collections of such cells were also found epidurally, particularly in the region of the mixed spinal nerve. In all ventral roots there were numerous fibers displaying advanced degenerative changes of the Wallerian type (Fig. 11*A*), an observation consistent with the degenerative changes in the anterior horn cells. Perivascular mononuclear cells, mostly lymphocytes, were encountered in occasional anterior roots (Fig. 11*B*). The endoneurium of several anterior roots contained fairly numerous petechiae. Dorsal roots, on the other hand, were free from change. Serial section of two dorsal root ganglia failed to reveal any abnormalities.

COMMENT

Clinical Considerations

A survey of the neurological signs and symptoms in this case revealed a close resemblance to those observed in many cases described in the Russian literature.§ According to Smorodintseff,[12] pareses and paralysis of the limbs, neck, and back, followed by progressive atrophy of the affected muscles, are common in this disease, much more frequent, in fact, than in the Japanese B and the St. Louis forms of encephalitis. The motor disability usually occurs on the second or third day of the illness, with "drooping neck" and paralysis of the muscles of the shoulder girdle among the most characteristic features.‖ Our patient had hemiparesis of the left side shortly after the onset of the illness, and bulbar paralysis became evident soon afterward. Then paralysis of the limbs and intercostal muscles set in. Respiratory failure was the immediate cause of death. The incubation period of the disease was 10 days, and thus our case runs true to type, for the corresponding Russian figures in fatal cases were 8 to 18 days (an average of 12 days). The illness in our case ran for 13 days, which is somewhat longer than the 1 to 8 days cited in the Russian literature.¶ The pathoanatomical basis of the hemiparesis was not determined. On the other hand, the paralyses in the realm of the bulbar and spinal nerves are readily explicable, for the respective nuclei displayed clear-cut cell loss with reactive gliosis, though inflammatory cell invasion was relatively slight.

Pathological Considerations

Postmortem studies revealed that we are concerned with strictly neurotropic virus in that the thoracic and abdominal viscera were unaffected except for pulmonary atelectasis and terminal bronchopneumonia, which were incident to the bulbar palsy. The lack of visceral lesions is in accord with other reports on this disease.

Cytogenesis and Pathogenesis of the CNS Lesions.—The lesions in the brain and spinal cord were much the same as those described in the Russian literature. The observations of Smorodintseff[12] and others that the lesions are virtually limited to gray matter were true in our case. There was widespread classic neuronophagia, especially in regions overrun by inflammatory cells. It seemed to us, as it has to others,# that the great majority of the mononuclear cells—usually decidedly pleomorphic—whether aggregated or diffuse, were hematogenous and/or adventitial in origin. The presence of intracytoplasmic free fat in cell aggregates, especially those in the cerebellar cortex, is not inconsistent with this view, as has been brought out by Spielmeyer.[18] This is not to say, however,

§ Summaries in English on the clinical and pathological aspects of this disease are to be found in the monograph by Silber and Soloviev[11] and in the article by Smorodintseff.[12]

‖ References 13 and 14.

¶ References 11, 12, and 14.

References 15 through 17. Kestner,[15] cited by Smorodintseff.[12]

that some of the cells were not reactive Hortega microgliocytes. On the other hand, Jervis and Higgins [5] favored the view that the majority of cells in the cell aggregates are microglial. The CNS possesses a notoriously poor defense against sudden attack in force, and thus must depend on help from vascular sources. The problem of genesis of the inflammatory and reactive cells in Russian spring-summer encephalitis appears to be no different from that in Japanese encephalitis,[19] except that in the Russian form the fundamental reactive process is more predominantly oligodendroglial. Leucocytic invasion of the brain has been observed in rapidly fatal cases.[16] In our case such cells were found perivascularly only in the cerebellum, and then were sparse. Clasmatodendrosis of astrocytes of the cerebral cortex reported by others [5] was not observed in our case. Coagulated edema fluid was found now and then in the brain tissue around vessels, and it is likely that the fluid was a factor in the pathogenesis of the perivascular lesions.[5]

Topography of CNS Lesions.—In an overall survey of the distribution of the lesions, as brought out in Figure 3, one is struck with the similarity which exists between this infection and Japanese B encephalitis. There are, however, some notable differences. In an examination of the brain in some 90 fatal cases of Japanese B encephalitis received by the Armed Forces Institute of Pathology, 16 of them proved by serological means, the cerebral cortex was seen to contain myriad cell nodules in virtually all sections. Even in cases in which survival was as long as 66 and 85 days, respectively, the scarred remains of mononuclear cell nodules could still be found in the cortex. In our case the great majority of sections from the cortex were free from invasive cells, a point which is in general agreement with reports from the Russian literature.* Only in the more anterior part of the island of Reil were significant numbers of invasive cells and proliferated glia found, and it is of interest that they were in the two or three laminae nearest the affected claustrum. By contrast, in the case reported by Jervis and Higgins [5] many large cells of the motor area were necrotic and were being phagocytosed, as in poliomyelitis, though some parietal areas were also affected. Jervis and Higgins also observed widespread perivascular cuffs of lymphocytes in the cortex, a finding which, judging from the literature, is uncommon in this disease.

Continuing the comparison, one finds that in Japanese B encephalitis the nuclei pontis are usually severely affected, whereas in our case they were almost spared. The inferior olivary nucleus frequently suffers rather little in Japanese B encephalitis, but in our case this nucleus was seriously damaged. In other instances of Russian spring-summer encephalitis the inferior olivary nucleus has also been a site of predilection.†

A highly conspicuous feature of our case was the cerebellar involvement. There were myriad mononuclear cell aggregates extending into the molecular layer from the region of damaged Purkinje cells, and the nuclei of the cerebellum were affected in similar degree. Japanese B encephalitis also has these characteristics. Reports emanating from Russia indicate that the degree of cerebellar involvement in spring-summer encephalitis varies considerably from case to case.[21]

Among the structures most seriously affected in our case was the anterior perforated substance. It is also a site of predilection in Japanese B encephalitis. Severe involvement of the thalamus and substantia nigra in our case runs true to the cases reported from Russia.[21] Jervis and Higgins [5] found that while the thalamus did contain inflammatory cells, it was considerably less affected than the cerebral cortex. They found little of note in the substantia nigra; and, as to the thalamus and lenticular nucleus and the adjacent white matter, they observed numerous, rather discrete, cell-invaded areas from which myelin had disappeared. The floor of the fourth ventricle and the reticular formation were much more heavily involved than in our case, while the inferior olivary nucleus in their case and in ours suffered equally. Jervis and

* References 12 and 17.

† References 16, 17, and 21.

Higgins commented that the lesions in the spinal cord were indistinguishable from those of poliomyelitis, a point with which we are in agreement.

Thus, the topography of the lesions in our case corresponds much more closely to that of the cases reported from Russia than that described by Jervis and Higgins.

Cranial and Spinal Nerve Involvement.— As was expected from the severity of involvement of the motor cranial nerve nuclei and the anterior horns of the spinal cord, advanced degenerative changes of the Wallerian type were noted in motor cranial nerves and in anterior spinal roots. It was of especial interest that inflammatory cells were present in these structures, but not in purely sensory cranial nerves or in dorsal spinal roots. We are, thus, dealing with a purely motor cranial nerve neuritis and spinal radiculitis. The presence of a purely motor neuritis and radiculitis is contrary to the observations of Russian authors,[22] who have pointed out that symptoms of sensory radiculitis are common. The two available posterior root ganglia in our case were free from changes, a finding which is in contrast to the observations of Russian authors [11] that they are frequently the seat of inflammatory cell infiltrates. Cranial nerves and sympathetic ganglia were not available to us, but inflammatory changes in these structures have been found by Russian workers [15] to be the rule.

Leptomeningitis. — Leptomeningitis was observed in all sections taken from the cerebrum, cerebellum, brain stem, and spinal cord, but it was severe only in the region of some of the cerebellar folia. Although perivascular lymphocytes could readily be found, the dominant cells were those of the histiocyte series, arising locally from the lining cells of the arachnoid trabeculae. This is the type of leptomeningitis, referred to by some as "acute serous meningitis," commonly encountered in Russian spring-summer encephalitis.[22]

SUMMARY

A laboratory worker exposed to air-borne Russian spring-summer encephalitis virus as a result of a laboratory accident became ill 10 days later and soon lapsed into coma. Hemiplegia and bulbar paralysis were early manifestations of the disease. Death occurred on the 13th day of the illness. Neutralization tests and complement fixation established the virus as the cause of the illness.

The neuropathological picture, similar in most respects to that described in the Russian literature, was characterized by involvement almost exclusively of the gray matter. Structures relatively spared were the cerebral cortex, caudate nucleus, putamen, and pars basilaris pontis. Most severely affected were the anterior perforated substance, thalamus, substantia nigra, globus pallidus, cerebellar cortex and nuclei, inferior olivary nucleus, medial vestibular nucleus, nucleus ambiguus, and anterior horns of the spinal cord. The sensory nuclei of the brain stem were, in general, much less affected than the motor.

Histologically the picture was very similar to that of Japanese B and other viral encephalitis, the only significant difference being that in Russian spring-summer encephalitis the oligodendroglia was much more implicated.

The peripheral nervous system was characterized by a purely motor neuritis and radiculitis in association with Wallerian degeneration emanating from necrotized nerve cells in the motor cranial nerve nuclei and anterior horns of the spinal cord.

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Treatment of Multiple Sclerosis with Low-Fat Diet

Results of Five and One-Half Years' Experience

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The primary purpose of this paper is to report the results of five and one-half years' experience of treating multiple sclerosis with a low-fat diet. A preliminary report of this method of treatment on the same patients was made two years ago.[1] At that time it was reported that during an average treatment period of nearly three years 45 patients with exacerbating-remitting type of multiple sclerosis seemed to benefit from the low-fat diet. This tentative assumption was based on a reduction in the frequency and severity of exacerbation of the disease and upon an increased performance of patients on the low-fat diet. The earlier cases seemed to benefit more than those with established disabilities. At that time possible theoretical reasons for employing the low-fat diet were discussed, and papers by me in collaboration with other investigators * bearing on our problem were reviewed in detail.

The secondary purpose of the present paper is to review in detail some recent observations of possible importance in the solution of our problem, and to amplify and evaluate my suggestion that the fat intake influences multiple sclerosis by altering the suspension stability of the blood.[1] The development in animals of increased adhesiveness and aggregation of the red blood cells and of an increased viscosity of the blood after large fat meals (Swank[4]; Swank and Cullen[5]; Cullen and Swank,[6] and Swank[7] will be of importance in the development of this hypothesis.

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From the Division of Neurology, University of Oregon Medical School; the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

* References 2 and 3.

MATERIAL AND METHODS

During the period from December, 1948, to July, 1954 (approximately five and one-half years) studies were initiated in 264 patients with multiple sclerosis at the Montreal Neurological Institute. All but a few of these patients were seen more than once; many of them were admitted to the Montreal Neurological Institute for diagnosis, and most of the remaining were seen by other neurologists. We have managed to maintain continuous contact with 210 of the 264 patients, and 158 of these have remained on the low-fat diet. The present report will deal mainly with the first 47 patients to be placed on the diet who remained on diet, and who have been followed closely for a period varying from four to six years.

Classification of Material.—The material has remained unchanged throughout the entire period of observation. Forty-five of the 47 patients had exhibited periodic exacerbations and remissions since onset of the disease. Early in the disease the remissions were often remarkably complete, and between attacks either the progress of the illness was stationary or the performance of the patient was improved. The length of this early period of disease was variable. Thirty-four of these patients were in this early phase of the disease when first placed on the low-fat diet.

The early phase of the disease usually passes insidiously into what I shall refer to as the late, or progressive, phase (exacerbating-remitting type—late progressive). This phase of the disease is characterized by gradually increasing disability or deterioration whether or not there are exacerbations of the disease. Patients are included in this category only when steady progression of the disease has been clearly established. Eleven patients were so classified at the time they were placed on the low-fat diet.

*Predietary and Dietary Data on Forty-Seven Patients**

Case No.	Sex	Performance Before L. F. D.				Age		No. of Exac. per Year		Years on L. F. D.	Performance on L. F. D.										Changes on L. F. D.						Lipid Intake Fat and Oil†	Comments
											End of 3½ Yr.				End of 5½ Yr.						End 3½ Yr.			End 5½ Yr.				
		Chair	Ambul.	W. P. T.	W. F. T.	Onset	L. F. D.	3 Yr. Prior L. F. D.	On L. F. D.		Chair	Ambul.	W. P. T.	W. F. T.	Bed	Chair	Ambul.	W. P. T.	W. F. T.		Unchan.	Impr.	Deter.	Unchan.	Impr.	Deter.		
											Exacerbating-Remitting Type—Early																	
1	F	..	..	+	..	22	26	1.3	0.2	5.4	..	..	..	+	..	..	..	..	+	..	+++ (N)	..	..	+++ (N)	..	30 + 15 Regular	Maj. op. No exac.
2	M	..	+	..	..	39	41	2.5	0.7	5.6	..	..	+	..	..	..	+	..	..	..	++	..	..	+	..	40 + 5 Irregular	Broke diet One exac.
3	M	..	..	..	+	28	30	2.0	0.4	5.0	..	..	..	+	..	..	+	..	..	..	..	+	..	..	++	30 + 15 Regular	Cont. steady progress
4	F	..	+	..	..	17	18	4.0	0.6	5.0	..	..	..	+	..	..	..	..	+	..	+++ (N)	..	..	+++ (N)	..	20 + 15 Regular	Dur. one exac. 6 hr.
5	M	..	..	..	+	36	48	0.3	0.4	5.0	..	..	..	+	..	..	..	..	+	+	..	..	..	..	+	40 + 15 V. irregular	.....
6	M	..	..	+	..	30	35	0.3	0.0	4.8	..	..	..	+	..	..	..	..	+	..	+ (N)	..	..	+ (N)	..	30 + 15 Regular	.....
7	F	..	..	..	+	29	43	1.0	1.0	5.7	..	..	..	+	..	..	..	..	+	+	(N)	..	+	(N)	..	20 + 10 Irregular	Broke diet 3 exac.
8	M	..	+	..	..	28	29	2.0	0.0	4.8	..	..	..	+	..	..	..	..	+	..	++ (N)	..	..	++ (N)	..	30 + 10 Regular	.....
9	M	..	..	+	..	24	27	1.3	0.2	4.9	..	..	+	..	..	..	..	..	+	..	..	±	..	..	±	20 + 10 Regular	Broke diet One exac.
10	F	..	..	+	..	26	29	1.0	0.0	5.8	..	..	+	..	..	..	..	+	..	+	..	..	+	..	..	50 + 15 Regular	.....
11	F	..	..	+	..	23	31	0.6	0.2	4.5	..	..	..	+	..	..	..	..	+	..	+	..	+	..	..	10 + 10 Regular	After preg. One exac.
12	F	..	+	..	..	27	33	0.3	0.0	3.0	..	..	..	+	..	..	..	..	?	..	++	..	..	..	..	.....	Status unknown 2 yr.
13	F	..	+	..	..	28	28	0.3	0.6	4.8	..	..	..	+	..	..	..	..	+	..	++	..	..	++	..	20 + 15 Regular	Broke diet—2 exac. Preg.—no exac.
14	F	..	+	..	..	33	35	0.8	0.6	5.0	..	..	..	+	..	..	..	+	..	..	++	..	..	..	+	40 + 10 V. irregular	.....
15	F	..	+	..	..	30	33	1.0	0.4	4.6	..	+	..	..	..	..	..	..	+	+	..	..	..	+	..	15 + 15 Regular	Broke diet 1 exac.
16	F	..	..	+	..	36	39	1.0	0.2	4.8	..	..	..	+	..	..	..	..	+	..	+	..	..	+	..	20 + 20 Regular	.....
17	F	+	..	..	..	28	34	1.3	0.1	5.8	..	+	..	..	..	..	+	..	..	..	+	..	..	+	..	15 + 15 Regular	Preg. No exac.
18	F	..	..	+	..	13	22	2.3	0.6	4.4	..	..	..	+	..	..	..	..	+	..	++ (N)	..	..	+	..	15 + 5 Regular	V. recent exac.
19	M	..	..	..	+	35	49	0.3	0.0	4.5	..	..	..	+	..	..	+	..	..	+	..	..	..	..	+	10 + 10 Regular	Slow progress
20	F	..	..	..	+	28	32	1.0	0.2	5.4	..	..	..	+	..	..	..	..	+	..	++	..	..	++	..	20 + 10 Regular	.....
21	M	..	+	..	..	31	35	2.0	0.2	5.3	..	+	..	..	..	..	+	..	..	..	..	+	..	..	++	50 + 5 V. irregular	Slow progress
22	F	..	..	..	+	28	33	0.6	0.2	4.7	..	..	..	+	..	..	..	..	+	..	++	..	..	++	..	15 + 10 Regular	.....
23	F	+	..	..	..	40	41	3.0	1.0	4.7	..	..	+	..	..	..	..	+	..	..	++	..	..	++	..	15 + 15 Regular	.....

24	F	..	+	..	..	40	46	0.6	0.0	6.0	..	..	..	+	..	..	..	..	+	..	++	..	..	++	..	15 + 10 Regular	.....
25	M	+	..	..	..	36	36	2.0	0.5	5.0	..	+	..	..	..	..	+	..	..	..	++	..	..	++	..	20 + 20 Regular	Broke diet One exac.
26	F	..	..	+	..	32	37	0.6	0.2	4.7	..	..	..	+	..	..	..	..	+	..	+	..	..	+	..	20 + 25 Regular	Broke diet One exac.
27	M	..	+	..	..	17	23	0.6	0.2	4.0	..	..	+	..	..	..	..	..	+	..	++	..	..	++	..	15 + 15 Regular	.....
28	M	..	..	..	+	26	27	2.0	0.0	4.0	..	..	..	+	..	..	..	..	+	..	+++ (N)	..	..	+++ (N)	..	.....	Status unknown 6 mo.
29	F	..	+	..	..	35	37	0.6	0.0	4.4	..	+	..	..	..	..	+	..	..	+	..	..	+	..	..	20 + 20 Regular	.....
30	M	..	..	..	+	34	40	0.6	0.0	4.4	..	..	..	+	..	..	..	..	+	..	++	..	..	++	..	20 + 20 Regular	Maj. op. & accidents No exac.
31	M	..	..	+	..	27	36	1.6	0.2	4.7	..	..	..	+	..	..	..	..	+	..	++	..	..	++	..	20 + 20 Regular	.....
32	M	..	..	..	+	27	29	1.0	0.0	4.0	..	..	..	+	..	..	..	..	+	..	+ (N)	..	..	+ (N)	..	20 + 20 Regular	.....
33	M	..	..	+	..	22	25	1.3	0.6	4.0	..	..	..	+	..	..	..	..	+	..	+ (N)	..	..	+ (N)	..	.....	Status unknown 6 mo.
34	F	..	..	+	..	27	31	0.6	0.2	4.0	..	..	..	+	..	..	..	..	+	..	++	..	..	++	..	20 + 15 Regular	Preg. One exac.
Exacerbating-Remitting Type—Late Progressive																											
35	M	..	+	..	..	28	43	0.0	0.0	5.5	..	..	+	..	..	..	..	..	+	..	+	..	..	+	..	50 + 40 Regular	.....
36	M	+	..	..	..	34	43	2.0	0.5	5.8	+	..	..	..	..	+	..	..	..	..	..	+	..	..	++	20 + 20 Regular	Slow progress
37	M	+	..	..	..	20	38	0.0	0.5	5.8	+	..	..	..	+	..	..	..	..	..	..	+	..	..	++	15 + 15 Regular	Slow progress
38	M	..	+	..	..	25	38	0.6	0.0	5.4	..	+	..	..	..	..	+	..	..	+	..	..	..	..	±	30 + ? Irregular	.....
39	M	+	..	..	..	26	34	1.0	0.0	4.4	+	..	..	..	..	+	..	..	..	+	..	..	..	..	+	15 + 15 Regular	.....
40	M	..	+	..	..	19	33	0.0	0.0	4.9	..	+	..	..	..	..	+	..	..	..	+	..	..	+	..	30 + 10 Regular	.....
41	F	..	+	..	..	29	37	2.0	1.0	5.0	..	+	..	..	..	..	+	..	..	..	..	+	..	..	++	40 + 15 Irregular	.....
42	F	..	..	+	..	31	49	0.3	0.0	4.0	+	..	..	..	+	..	..	..	..	..	..	++	..	..	+++	.....	Off diet 2 yr.
43	M	..	+	..	..	30	39	0.3	0.0	5.4	..	+	..	..	..	..	+	..	..	+	..	..	..	..	±	20 + 20 Regular	.....
44	F	..	..	+	..	18	38	0.0	0.0	5.0	..	..	+	..	..	..	+	..	..	+	..	..	..	..	±	30 + 10 Irregular	.....
45	M	..	+	..	..	22	28	0.6	0.2	4.4	..	+	..	..	..	..	+	..	..	..	..	+	..	+	..	15 + 15 Regular	.....
Progressive Type—No Exacerbations																											
46	M	..	..	+	..	44	51	0.0	0.0	4.4	..	..	+	..	..	..	..	+	..	+	..	..	..	..	+	30 + 5 Irregular	Off diet 1-2 yr.
47	M	..	..	+	..	34	44	0.0	0.0	4.8	..	..	+	..	..	+	..	..	..	..	..	+	..	..	++	20 + 20 Regular	.....

* These patients are the same as those included in Charts 1 and 2 of the preliminary paper.[1] Under the heading "Performance Before (or "on") L. F. D. (low-fat diet)," Chair indicates that the patient was confined to a chair; Ambul. indicates the patient was ambulant; W. P. T. indicates that the patient was working part time, and W. F. T. indicates working full time. In the column headed by "Changes on L. F. D.," Unchan. means the condition of the patient was unchanged; Impr. indicates improvement, and Deter. indicates deterioration. (N) indicates normal neurological examination.

† The lipid intake is in grams per day.

Only two of the patients had steadily progressive disease from onset and did not exhibit clear-cut "attacks" (exacerbations and remissions) at some time (progressive type—no exacerbations).

Forty-one of the patients were ambulant and working part or full time when they were placed on the diet. In a sense the patients were selected in an attempt to have as many active, working patients as possible under our care. This was done for two reasons: First, it is far easier to evaluate an exacerbation or a remission in an ambulant patient, and, second, the disease seems to be more rapidly progressive in ambulant, working patients than in those confined to the wheel chair or to bed.

Control Material.—During the first years of our study we did not have a large enough group of patients with multiple sclerosis who consumed a normal diet to serve as a control for those who received the low-fat diet. We therefore used the three-year period preceding the low-fat diet as a control for each of these patients. These data, with other pertinent facts concerning each patient, and the classification of each patient are included in the single Table in the present paper, and in Charts 1 and 2 of the preliminary report.[1] The frequency and severity of "attacks" of the disease and the general over-all performance of the patient have been used in evaluating the course of the disease before and after going on the diet.

There has been no change during the five-and one-half-year period in the control of this material. The patients reported at the present time were the same ones reported two years ago. They were interviewed at regular intervals by the same observers during this period. In so far as possible, their progress, including exacerbations and remissions, has been evaluated exactly as before.

The Low-Fat Diet.—The diet has also remained unchanged except for minor alterations in the prescribed amounts of the fat intake. During the first year the diet contained 20-30 gm. of fat, mostly milk and animal fats. In the subsequent two years the saturated animal and milk fats were limited to 20 gm. daily. To this was added 5 gm. of cod liver oil and 10-15 gm. daily of vegetable oil or fish oil. At the end of approximately three years milk fat was eliminated from the diet completely, and the prescribed total fat intake was reduced to 30 gm. daily. Since then the diet has contained 15 gm. of animal or hard fat (included hydrogenated vegetable oil, such as shortening and margarine) and 15 gm. of vegetable or fish oil. The protein intake has been maintained at 50-60 gm. or more daily, depending upon the weight and dietary habits of the patients, and the balance of the caloric need has been obtained from carbohydrates. The caloric intake has been the same throughout the entire study. Our records would indicate that the average caloric intake of the women was 1700 Cal. for a 130 lb. woman, and 1900 Cal. for a 145 lb. man. These figures may be low, since the patients were concerned primarily with recording the fat intake and may have forgotten to record other foods at times. On the whole the patients have remained 5% to 10% under what might be considered normal average weight. One multiple vitamin capsule, containing vitamins A, B, C, and D complex, is taken daily, and whole wheat bread is recommended. Skim milk is used by all patients as a source of protein. Most patients eat at least one egg daily.

The dietary intake of the patients is checked every two weeks at first and later at monthly intervals. The patient records all the food he eats for each meal in a notebook provided for this purpose. From this the dietitian determines the food intake and makes necessary adjustments. The patient's weight is checked at each visit, and rapid changes in weight are carefully watched for. The diet is mimeographed (Appendix), and special recipes substituting vegetable oils for animal and butter fats have been assembled and are furnished to the patient.

Various supportive measure, such as physical therapy, use of drugs to relieve nervous tension, and other medical treatments, have been employed as indicated. In this group of patients none of the ambulant and only a few of the nonambulant patients have received physical therapy regularly.

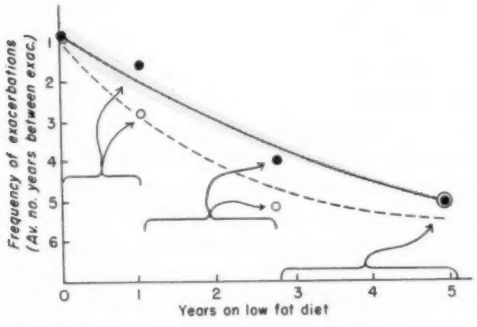
RESULTS

We have been able to follow continuously for four to five and a half years, and at regular intervals, all but 3 patients in the group of 47 included in Chart 1 of the previous paper [1] and in the Table of the present paper. Of the three patients whose status is no longer known, one has been off diet and out of touch with us for two years, and the other two have been out of touch with us for six months.

Effect of Low-Fat Diet on Severity and Frequency of Exacerbations of Disease.—Detailed data concerning each patient are included in the Table. Reference to the Chart in the preliminary report [1] gives additional data concerning the frequency of exacerbations of disease during the first three and a half years on diet and prior to going on diet. The Table in the present paper shows that there has been a marked reduction in the frequency of exacerbations while on the low-

fat diet. This is indicated under the heading "Number of Exacerbations per Year."

Exacerbating-Remitting Type—Early Phase: The reduction in frequency rate of exacerbations is shown schematically in the Figure. An average of one exacerbation every 10 to 11 months occurred during the three-year period before the patient's going on diet. Thygesen [8] reported a similar average exacerbation rate in his patients receiving no treatment. During the first year on diet all patients in this group had an average of one exacerbation every 18 months. When those patients whose exacerbations occurred after they had exceeded the prescribed dietary intake by approximately 100% for a week or longer are eliminated, the average period between exacerbations was 34 months (circles in Figure). During the period from the end of the first to the end of 2.8 years (the average duration of treatment reported before [1]) the average period of time between exacerbations in the early group was approximately 45 months. When those whose exacerbations occurring after dietary indiscretions are eliminated, the period between exacerbations is approximately 60 months. During the period from the end of 2.8 years to the end of 4.9 years (the average total duration of treatment) the average period of time between exacerbations was 57 months. In no instance in this last period, of two years, could the few exacerbations be clearly correlated with dietary indiscretions.



Schematic presentation of the change in frequency and severity (width of stippling) of exacerbations during the five-year period on diet. The dots (and solid line) indicate the frequency of exacerbation when no correction is made for exacerbations occurring after dietary indiscretions. The circles (and broken line) indicate the average frequency of exacerbations when exacerbations following dietary indiscretions are eliminated from the analysis.

There was also a significant decrease in the severity of the exacerbations during the period on the diet, and this became more marked the longer a patient was on the diet. This is shown schematically in the Figure by the width of the area of stippling on either side of the solid black line. Many of the exacerbations during the second, third, fourth, and fifth years on the diet were very mild and of a few hours' or few days' duration, and the added disability usually cleared entirely.

Late Progressive Phase of Exacerbating-Remitting Type of Multiple Sclerosis: In this phase an even greater reduction in frequency and severity of the exacerbations occurred during the period on diet. This change was also cumulative in the sense that the longer patients were on diet the less frequent were the exacerbations. During the last two years on diet, only two exacerbations were experienced by the 11 patients in this group, and these were mild.

Progressive Type with no Exacerbations: In this type the disease continued to progress slowly and relentlessly despite the absence of exacerbations.

Effect of Low-Fat Diet on General Performance of the Patient.—Early Exacerbating-Remitting Type of Multiple Sclerosis: Nine patients in this group were working full time prior to going on diet. At the end of our first three and one-half years of experience with this diet (the average duration of treatment was 2.8 years) 24 patients were working full time. At the present time, at the end of five and one-half years of experience (the average duration of treatment is 4.9 years), 23 patients are known to be working full time, and the status of 1 other patient, who at the end of three and a half years was working full time, is no longer known to us. If the patient whose status is unknown to us is eliminated from the survey at this point, the same number of the patients working full time at the end of three and one-

half years on the diet are working full time now. Twenty of these are the same patients. In six instances the performance category has changed; in three it has improved, and in three it has gotten worse.

At the completion of three and one-half years on the low-fat diet nine patients had improved sufficiently to be considered normal neurologically. Two years later eight of these patients were still normal neurologically. One patient who had a recent exacerbation could not be considered completely normal four months after this exacerbation, although the only neurological deficit which was present consisted of generalized weakness and very slight tremor. Hyperactive reflexes, nystagmus, and other signs considered significant in multiple sclerosis were as yet absent. Three additional cases have shown definite deterioration at the end of five and a half years. No patients in this early group have become chair-ridden or bedridden while on the low-fat diet.

Late Progressive Phase of the Exacerbating-Remitting Type of Multiple Sclerosis: At the end of three and one-half years 4 of these 11 patients were chair-ridden. At the end of five and one-half years two of these chair-ridden patients have now become bedridden and two have remained chair-ridden. Two other patients who were working part time at the end of three and one-half years are no longer working and are classified as ambulant. No patients in this group were working full time at the end of three and one-half years, but at the present time one patient is working full time.

There has been evident deterioration, although not marked, in this group of patients. During the first three and one-half years five patients deteriorated. During the subsequent two years three more patients can be added to this group. At the end of three and one-half years four patients had maintained their status while on low-fat diet, but now, at the end of five and one-half years, all patients have shown either deterioration or improvement; three patients have shown slight improvement, and eight have shown definite deterioration.

Progressive Type—No Exacerbations: Both patients in this classification have deteriorated steadily.

Importance of Strict Dietary Control.—The last two years of experience with the low-fat diet has emphasized the importance of rigid dietary control if maximum benefit from the low-fat diet is to be obtained. It is quite possible that the greater incidence of exacerbations during the first year on diet resulted from dietary laxity due to indiscretion, or to inability to follow the diet closely during the first year. This possibility is supported by the impression that those patients who follow the diet closely have in general done much better than those either incapable of following, or unwilling to follow, the diet carefully. However, it is my impression, based on the fact that many patients followed the diet carefully from the beginning, that much of the improvement in later years has been due to a cumulative effect of the low-fat intake.

It is a continuing observation that those patients who remain underweight by all accepted weight-height standards do better than those who are overweight or who gain weight. The majority of our patients were underweight when the low-fat diet was initiated, and many lost 5-10 lb. during the first two months on the diet. The weight usually stabilized at that point and remained stationary. Exacerbations of disease have followed unexplained rapid loss or gain in weight frequently enough that we now watch the patient's weight carefully. On the other hand, many patients have a tendency to consume less fat than prescribed, particularly when they first go on diet. This may cause them to feel weak and listless, and in some instances has been the reason for abandoning the diet.

GENERAL EVALUATION OF RESULTS

During the past two years it has become increasingly evident that the low-fat diet used in this study was beneficial to a large percentage of the 47 patients with multiple sclerosis observed during the four- to five-and-one-half-year period. It is now clear that

the benefit was derived particularly by those in whom the disease was in its early phase. During the past two years there has been little further deterioration in this early group of patients. In the late progressive cases, however, continuing deterioration has been the rule, although this deterioration has been slow in most of the patients. It is likewise clear that the disease has not been cured by the low-fat diet even in the early cases, since clear-cut exacerbations were noted in all classes of patients on the diet. A reduction in the severity and frequency of the exacerbations has been substantial, and, despite the recurrence of minor exacerbations, most of the patients have improved generally and have become capable of increased work during their period on the diet. It is abundantly clear that if the course of this disease is to be significantly altered treatment must be started early.

It is unfortunate that a parallel control group of patients has not been under observation. This was found to be unattainable at the beginning of our study. However, the fact that the frequency and severity of exacerbations steadily decreased over a period of five and one-half years strongly indicates that the low-fat diet altered the course of the disease. Even so, in a disease with an average natural course of possibly 20-25 years [9] it is impossible to predict the total duration effect of a therapy which has been used for only five and a half years. We intend to follow these patients for another five years on the low-fat diet in the hope that we can establish whether or not the apparent improvement in the course of the disease is permanent.

We now have records of 52 patients a few of whom went off the diet, but most of whom, for various reasons, never received the low-fat diet. Unfortunately, these are not satisfactory for control, for several reasons. First, they have not been followed as long as those on the low-fat diet. More important, however, they are neither paired nor alternate controls, and are therefore "selected." It is quite possible that some of these patients went off the diet because they were doing poorly, and others were unable to follow the diet. In general the patients in this group have done poorly.

Sixteen of these 52 patients have been under periodic observation for four years or longer. When first seen, 14 of these were ambulant, 1 was in wheel chair, and 1 was confined to bed. All but 1 of these 16 patients have shown significant deterioration: Eight are now ambulant, two are confined to a wheel chair, and six are bedridden. Only on the basis of length of follow-up can these 16 patients be compared with the 47 patients on low-fat diet reported in detail in this paper.

We have also approximately 111 patients who have been on diet for a few months to just under four years who are not the subject of the present report. In general they have done well, those who have been on diet the longest doing best. These patients are not reported at present, but will continue to be followed with those reported in detail in this paper for another five years.

STATISTICAL ANALYSIS OF RESULTS

Statistical assessment of the results of this "experiment" is directed to the question, "What is the average reduction in exacerbation frequency to be expected from the low-fat diet?" We take as our basic observation the difference, for each patient, between his prediet and his on-diet exacerbation frequency rate. It is first necessary to deal with the skewness of distribution of these differences. A simple graphic plot of the cumulative frequency distribution on log probability paper shows good fit to a straight line, thus confirming our suspicion that the distribution of observed frequency differences may be log-normal. In this case it is possible to transform our differences by using their logarithms, which will be normally distributed. We can then apply the elementary "Student" statistics for a mean difference, which would be inappropriate for use on the skewed distribution. As a convenience in calculation, the constant 2 has been subtracted from all the differences so as to make them all of the same sign before obtaining their logarithms.

Proceeding with the calculation of the mean, standard deviation, and standard error of these transformed differences, we obtain the following statistics for the 44 patients of the exacerbating-remitting type (early and late), where p is the average annual prediet exacerbation frequency rate, and d is the average annual rate for the five years on the low-fat diet.

	Log $(d-p-2)$	Net Difference $(d-p)$ in Original Units of Exacerbations per Year
N	44	.....
Mean	0.44368	—0.78
Standard deviation of individual patients	0.12695	.....
Standard error of mean	0.01914	.....
For individual patients (95% tolerance limits [10])		
Central 75% range of net difference	0.26366 to 0.62370	+0.02 to —2.21
Central 90% range of net difference	0.18635 to 0.70101	+0.47 to —3.02
Central 95% range of net difference	0.13710 to 0.75026	+0.63 to —3.63
For average patient		
75% confidence limits on mean net difference	0.42129 to 0.46607	—0.64 to —0.93
90% confidence limits on mean net difference	0.41128 to 0.47608	—0.59 to —0.99
95% confidence limits on mean net difference	0.40500 to 0.48236	—0.54 to —1.04

The tolerance limits for individual patients show the range within which the central 75%, 90%, and 95% of patients of this kind may be expected to fall in 95% trials of this kind. Thus, we can be "95% confident" that the central 95% of multiple sclerosis patients subjected to trials identical to this one will show net differences in exacerbation frequency rates better than +0.63 and up to —3.63. The confidence limits for the mean show the limits within which the group mean of all patients would be found to lie in 75%, 90%, and 95% of such group trials. Thus, we can be "95% confident" that the true mean experience of all such patients subjected to trials of this sort would be better than —0.54 and up to —1.04 exacerbations per year for the diet-prediet difference.

From these statistics it can be seen that the effect of the low-fat diet on the frequency of exacerbations in the average patient is almost certain to be beneficial. A net decrease in frequency of between 0.54 and 1.04 exacerbation per year can be expected in the average patient. Since this confidence interval does not include zero, the average net effect is called statistically significant. It is of sufficient magnitude to be of clinical interest as well. Individual patients, however, are subject to a very wide range of effect of the low-fat diet—from an increase of about half an episode a year to a decrease as great as 3.6 a year.

These 44 patients have been on the low-fat diet about 5 years (actual mean equals 4.96 years). Assuming that during this period the effect of the diet is cumulative and linear, we could expect an average net change of —0.15 episode per year. It is of interest to ask how early one might have been able to detect a statistically significant average net effect? Our observed difference at five years, —0.76, is about four times the minimum difference required for statistical significance. It can be estimated [11] that a just significant difference could have been detected on our sample after about 1.5 years' experience on the low-fat diet. With a smaller sample, say, 20 patients, it would have required 3 years to obtain a just significant difference, and some 11 years to obtain as significant a difference as has been observed in these 44 patients.†

It should be noted that we have recorded as exacerbations, fluctuations in severity of the disease that the patients were not always inclined to consider exacerbations. Furthermore, in our statistical evaluations we have included even those exacerbations occurring after dietary indiscretions for the reason that we have no way of knowing just what constitutes a significant dietary indiscretion. These factors would tend to strengthen the results of our statistical analysis by an amount which is unknown, and possibly sig-

† Dr. Carl E. Hopkins, biostatistician to University of Oregon Medical School, made the statistical analysis of the data included in the Table.

nificant. It should further be noted that the statistical analysis is only a partial analysis of the effects of the low-fat diet on multiple sclerosis in that it does not consider the reduction in severity of exacerbations, which was possibly more impressive than the decrease in frequency of the exacerbations.

When exacerbations occurring after dietary indiscretions are eliminated, our data also suggest the possibility (Figure; broken line) that the net effect of the diet was to produce a maximum reduction in frequency of exacerbations by the end of the first three years. In the subsequent two years the exacerbation rate remained unchanged.

COMMENT

The observations reported in the present paper indicate that the low-fat diet was beneficial during an average observation period of approximately five years to a very large proportion of our 47 patients with multiple sclerosis. The period of observation has now been sufficiently long to give us some confidence in our observations. Even so, it must not be overlooked that since we are dealing with a disease having an average duration of perhaps 20 to 25 years, any conclusions concerning its therapy must still be tentative.

It appears that the benefit derived from the low-fat diet was due to a lessening of both severity and frequency of exacerbations of the disease. In the early cases this seems to have altered the course of the disease significantly. In the more advanced cases, even though the exacerbations were very mild or infrequent, or absent, the existing disabilities steadily worsened. New signs and symptoms were seldom seen. In the absence of appropriate pathological studies, one can only speculate whether the steadily increasing disabilities in these cases are due to the development of new lesions, to extension of old lesions into surrounding undamaged nerve tissue, or to a progressive hardening of old sclerotic areas.

The apparent freedom of many of the earlier cases from either exacerbations or steady progression of disease suggests that in these cases new lesions were not developing. In almost all advanced cases, on the same rigid dietary control, the disabilities progressed slowly and relentlessly. This leads one to wonder if the lesions of multiple sclerosis, once established, or once having reached a critical point in their development, are not capable of further progression independent of the underlying metabolic defects in the disease. One can only speculate about the mechanism of this progression. Is it due to a continued sclerosis of the lesions, or possibly to "fatigue," then organic deterioration, of the remaining neurons?

Detailed and extensive studies of the content of the various lipids of the blood (cholesterols, phospholipids, fatty acids, and neutral fats) have revealed no essential differences between normal subjects and patients with multiple sclerosis (Wilmot and Swank [12]). Both groups when placed on the low-fat diet exhibited little sustained change in the chemically determined lipidol fractions except a decrease in cholesterol. Examination of the blood microscopically in dark-field illumination, however, showed that the number and size of the chylomicra present in the blood at any time of day was significantly decreased both in normal subjects and in patients with multiple sclerosis when on low-fat diet.‡ It would seem that any improvement in multiple sclerosis in patients on the low-fat diet is not due to a lowered fat content in the plasma. These studies do not rule out the possibility that the rate of fat metabolism is a factor in the severity and frequency of multiple sclerosis.

The hypothesis has already been developed that the neurological lesions in multiple sclerosis may be due to tissue ischemia resulting from a breakdown of the suspension stability of the blood.[1] It was suggested that this altered state of the blood is precipitated by large fat meals in persons presumed to possess an inherent metabolic defect. It might be of value to review and evaluate this point of view in the hope of throwing light on our problem.

‡ Unpublished observations. Reference 12.

Reasons to suspect a vascular component in the pathogenesis of the lesions of multiple sclerosis have been previously outlined.[1] Aside from the clinical features discussed at length by Putnam [13] and Brickner,[14] the following observations indicate the presence of generalized vascular factors in multiple sclerosis. Tortuous and irregular blood vessels have been observed in the nail bed by Gomirato [15] and Chiavacci and Putnam,[16] and these and other peripheral vascular phenomena have been described and discussed by Grain and Jahsman.[17] The fact that many other conditions exhibit similar vascular phenomena is indicative of the complexity of our problem, rather than of a lack of significance of the changes. Franklin and Brickner [18] observed spasms of the retinal arteries during transient episodes of scotoma in patients with multiple sclerosis, and Rucker [19] and Haarr [20] observed sheathing of the retinal veins in cases of multiple sclerosis. To these observations can be added the increase in capillary fragility reported recently by Shulman, Alexander, Ehrentheil, and Gross.[21] The relationship of the lesions to central veins in the central nervous system is an old observation emphasized recently by Putnam,§ Dow and Berglund,[24] and Fog.[25] To this can be added the observations of Macchi [26] that vascular pathology is frequently present in the central nervous system of subjects with multiple sclerosis. Macchi observed stasis and congestion of the venules and capillaries, proliferation of the adventitia, formation of new blood vessels, and perivascular and pericapillary infiltration of round exudative cells, and sometimes of perivascular hemorrhages. In many respects these changes are similar to those observed by Swank and Hain [27] and Lewis and Swank [28] in the brains of dogs after injections of microemboli into the cerebral circulation.

Other observations indicate that changes occur in the blood itself in multiple sclerosis. Fog [29] noted conspicuous decreases in the number of the circulating thrombocytes in patients with multiple sclerosis during activity of the disease, and Nathanson and Savitsky [30] reported that the platelets are abnormally adhesive in cases with multiple sclerosis.

In recent studies, Swank, Franklin, and Quastel [31] observed abnormal plasma protein patterns in paper chromatograms in patients with multiple sclerosis during acute exacerbations of the disease. Subsequently, Swank [32] studied the plasma protein patterns in paper chromatography at weekly periods in 21 normal subjects (243 chromatograms) and in 41 patients with multiple sclerosis (437 chromatograms). The periods of study varied from a few weeks to as long as four months. A high incidence of abnormal chromatograms was observed in patients with multiple sclerosis. These abnormal patterns tended to recur in cycles every one to three months and were present for periods of one to four or five weeks. Thirteen instances of clinical activity of the disease were noted, and in 12 of these the activity was concurrent with, or in close association with, the periods when the chromatograms were abnormal. However, many abnormal chromatograms were present without accompanying clinical activity of the disease. Similar, but much less marked cyclic changes in the plasma proteins were observed in normal subjects. During the common cold and during menstruation, the chromatograms tended to be abnormal, and in one normal subject and in two normal sisters of patients with multiple sclerosis abnormal chromatograms were frequently seen. It was felt that this study indicated a close relationship between activity of multiple sclerosis and abnormal plasma proteins. No specific protein abnormality could be identified, however. By means of the ultracentrifuge, Aird, Gofman, Jones, Campbell, and Garoutte [33] observed frequent abnormalities of the plasma lipoproteins in patients with multiple sclerosis, particularly during exacerbations of the disease. By means of the electrophoresis technique Saifer, Rabiner, Oreskes, and Volk [34] also found that the plasma proteins in multiple sclerosis may be abnormal. These observers found a signifi-

§ References 22 and 23.

cantly decreased albumin and A-G ratio, and significantly increased alpha-2 and beta globulin fractions in about 90% of their patients with multiple sclerosis. They also observed frequent positive reactions with the cephalin-cholesterol flocculation test and moderately frequent positive reactions with the thymol turbidity test. They did not relate these abnormalities to exacerbations of the disease or to activity of the disease. Electrophoretic fractionation of the serum proteins by Bernsohn and Cochrane [35] also revealed a high incidence of alterations in the electrophoretic pattern of the plasma proteins in multiple sclerosis. The changes they identified consisted of an increase in alpha-2 globulin with concomitant reduction in the albumin component. In 15 of their 27 cases they also observed a double peak in the alpha-2 globulin fraction. Despite the fact that some investigators have not observed abnormalities in the plasma proteins in multiple sclerosis (Dobin and Switzer [36]), the total evidence indicates that the plasma proteins are abnormal frequently in this disease. In addition, observations of Swank [32] suggest the possibility that plasma protein changes may be a factor in the fluctuating course of the disease (exacerbations-remissions). Further studies will be necessary, however, before the relationship of the plasma proteins to the pathogenesis of the disease can be defined.

Still other observations suggest that abnormalities may be present in the physical state of the blood in cases of multiple sclerosis (Kniseley and co-workers [37]; Roizin, Abell, and Winn[38]). These investigators observed "sludging" of the blood in the vessels near the cornea of the eye in patients with multiple sclerosis. Unfortunately, the magnification and resolving power at present available for studies of the circulation of the blood vessels of the sclera are not adequate to recognize clearly more than aggregation of the red blood cells. Abnormal adhesiveness cannot be identified by this technique. Clumping or aggregation of the red blood cells in the veins of the sclera has been observed by Kniseley and his colleagues in many unrelated conditions, and this phenomenon can be induced experimentally in animals by vasoconstrictor substances and by stimulation of vasoconstrictor nerves (Fowler [39]). Before the so-called "sludging" phenomenon can be considered an etiologic factor in multiple sclerosis, it is imperative that this phenomenon be shown to be of pathogenic significance. This has not been possible with the methods utilized for these studies in the past.

Aggregation, and also adhesiveness, of the red blood cells occur in the hamster after large fat meals (Swank and Cullen [5]; Cullen and Swank [6]). With use of a method for measuring the viscosity which I developed in collaboration with Dr. John Roth,[40] it was shown that the adhesiveness and aggregation of the red blood cells which appear after large fat meals are accompanied by significant increases in viscosity of the blood (Swank[7]). These studies suggest that if adhesiveness as well as aggregation of the red blood cells is present in the venous circulation, significant elevation of the viscosity of the blood may also be present. One might therefore expect to find the blood viscosity elevated in patients with multiple sclerosis if the aggregates of red blood cells were abnormally adhesive for one another.

To test this hypothesis, the viscosity and the hematocrit reading of the venous blood of 33 patients with multiple sclerosis and of 33 normal (control) subjects were studied at intervals of one week for four to six weeks.‖ The relationship of the viscosity to the hematocrit reading in the control group was found to be approximately the same as in the patients with multiple sclerosis. These observations do not rule out the possibility that abnormal stickiness of the red blood cells for one another and for the vascular endothelium in the capillary bed may have been present, but they would seem to suggest that the aggregates observed by Kniseley [37] and by Roizin, Abell, and Winn [38] in the venous

‖ These observations are to be published separately.

circulation were not usually the result of abnormal adhesiveness of the red blood cells for one another. Possibly they were related to emotional tension and physiological factors known to cause physiological aggregation of the red blood cells,[39] or to other factors as yet not identified. It should be pointed out that in none of our patients was the viscosity determined during the exacerbation of the disease. Roizin, Abell, and Winn [38] have indicated that the "sludging" was present during a very high percentage of their examinations. If adhesiveness as well as aggregation of the red blood cells had indeed been present, we should have expected to find the blood viscosity elevated a significant number of times in the patients with multiple sclerosis. It would appear that both the genesis and the significance of "sludging" of the red blood cells have yet to be established in multiple sclerosis.

In previous papers ¶ it was shown that the incidence of multiple sclerosis is high in high fat-consuming areas of the world, and low in low fat-consuming areas. Furthermore, clinical studies reported in this paper have indicated that the course of this disease may be altered favorably by placing patients with multiple sclerosis on a low-fat diet. These data, plus the changes in the physical state of the blood produced by fat ingestion already described in this paper,# suggest a close relationship of these factors. The changes in the blood observed in the cheek pouch of the hamster after large fat meals are very similar, if not identical, to the "sludging" described by Kniseley in his original experiments.[41] In view of the observations of Roizin, Abell, and Winn,[38] and the theoretical considerations in this paper, it is tempting to jump to the conclusion that "sludging" of the blood is a factor in multiple sclerosis. However, to do this in the absence of clear-cut indications would be misleading. It might be well to review briefly the early changes observed in the cheek pouch of the hamster after the ingestion of large fat meals. The earliest change consists of increased stickiness of the red blood cells for one another and for the vascular endothelium. This occurs prior to any large-scale aggregation of the red blood cells and results in a visible slowing of the circulation. At frequent points red blood cells can be seen sticking to the endothelium, often in masses which nearly occlude the vascular lumina. Such a change might often have the effect of retaining a large number of red blood cells in the peripheral circulation. This would reduce the hematocrit readings in the venous blood, and would tend to reduce rather than increase the viscosity of the venous blood, since the vicosity of the blood is related directly to the hematocrit values. This degree of breakdown of the suspension stability of the blood might conceivably be present in the absence of observable changes in the venous or arterial circulation. In any event, it seems likely to me that further experiments will be necessary before the status of "sludging" of the blood in multiple sclerosis can be determined.

If a high-fat intake is indeed a precipitating factor in multiple sclerosis, our studies would indicate that other factors, as yet not clearly defined, may also play a part in the pathogenesis of this disease. In a previous paper [1] attention was called to the possible relationship of rapid and frequent changes in the weather to activity of the disease. At present a detailed study is being made of the relationship of the weather during the past five years to activity of multiple sclerosis in the Montreal area. The results are not yet available for publication. I feel that undue fatigue, particularly if chronic, and nervousness are factors deserving serious consideration.*

*Miss Aagot Grimsgaard assisted in the dietary control and the follow-up of the patients.

CONCLUSION

Five and one-half years' experience with a low-fat diet in the treatment of multiple sclerosis is summarized. This diet appears to lessen the severity of the disease by re-

¶ References 2 and 3.

References 5, 6, and 7.

ducing the frequency and severity of the exacerbations. Its usefulness is greatest early in the disease, before significant disability and a steady progression of symptoms have developed. The period of observation has now been sufficiently long to give us some confidence in our observations, although we must not overlook the fact that since we are dealing with a disease having an average duration of perhaps 20 to 25 years, any conclusion concerning its therapy must still be tentative.

The mechanism by which the fat intake might influence the disease is discussed. Serious consideration is given to the hypothesis that patients with multiple sclerosis have a basic defect in the suspension stability of their blood, which is upset by the hyperlipemia following heavy fat meals.

APPENDIX

Low-Fat, High-Carbohydrate, Moderate-Protein Diet

Your diet will contain 3 tsp. (15 gm.) of hard fats (animal fats, margarine, lard, and shortening) and 3 tsp. (15 gm.) of vegetable oil or a substitute a day. In so far as possible, the intake of fat should be evenly distributed throughout the day. All patients should consume at least one egg and 1 tsp. (5 cc.) of cod liver oil daily. Fats or oils used for cooking or baking must be included when determining the daily fat intake.

Foods forbidden on your diet

Whole milk, butter, cream, cocoa, and chocolate, and all foods containing these substances, such as pastries, pies, steamed puddings, cake puddings, cakes, cookies, doughnuts, chocolates, chocolate bars, cocoa, hot chocolate, chocolate-flavored drinks, cheese, ice cream, and cream sauce made with butter and/or whole milk, and canned spaghetti with meat or meat sauce.

Foods permitted in any quantity

Boiled codfish, halibut or haddock, scallops, lobster, crab — any fish which contains no oil
All vegetables
All clear soups
White or brown bread
All cereal products
Skim milk, at least 3 glasses a day or
Buttermilk
Cottage cheese
All fruits
Desserts made from egg whites
Cream soup made with skim milk
Maple and corn syrup
Water ice
Rice, tapioca, or cornstarch puddings made with skim milk, no egg yolk
Jello
Fruit juices
Vegetable juices
Clear tea or coffee
Carbonated beverages
Jam and jelly
Molasses
Marmalade and honey
Sugar
Spaghetti and macaroni
Fresh or tinned clams and oysters
Seasonings

Foods permitted in limited quantity

Soda crackers
Graham wafers
"Social Teas"
Arrowroot biscuits or Tiz biscuits

Substitutes for 1 tsp. of hard fat

2 oz. (60 gm.) chicken, beef, roast leg of lamb, ham, veal, beef sausage, liver, and turkey
1 egg
3 slices bacon, fried crisp and drained well
1 slice of Bologna, salami, or liverwurst (1 oz.)
1 frankfurter
1 pork sausage
1 slice of roast pork (1 oz.)
1 oz. goose or duck
1 tsp. margarine, lard, or shortening
½ lamb chop (1 oz.)
½ pork chop (1 oz.)

Substitutes for 1 tsp. of vegetable oil

1 tsp. of olive oil, corn oil, cottonseed oil, wheat germ oil, Mazola and Wesson oil, cod liver oil
5 olives
2 tsp. of salad dressing or mayonnaise
15 peanuts
2 tsp. pure peanut butter (not hydrogenated)
2 oz. tuna fish or trout
2 oz. of canned or fresh salmon
1 oz. of mackerel
1 oz. of herring, sardines, or kippers
4 small anchovies

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Antibrain Antibodies in Multiple Sclerosis

Study of the Antibrain Antibodies in the Blood of Multiple Sclerosis Patients by Complement Fixation Tests

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This study is based on the premise that the serum of a multiple sclerosis patient may contain antibrain antibodies and that the disease is of an allergic nature. The etiology of multiple sclerosis being unknown, it was thought desirable to explore the possibility of a specific reaction of the blood sera of multiple sclerosis patients with the antigens prepared from the multiple sclerosis brains. Specific serologic studies in multiple sclerosis have been reported by Sachs and Steiner,[1] Steiner,[2] Frick,* and others. Acute disseminated encephalomyelitis accompanied by production of antibrain antibodies has been induced in animals by injection of emulsions of normal homologous and heterologous brain or spinal cord tissues, with or without adjuvants.† The production of these antibodies in the monkey was reported by Kopeloff and Kopeloff.[9] Schwentker and River [10] produced antibody response in the rabbits by injections of emulsions of homologous brain. Hill [11] demonstrated complement-fixing antibodies but did not demonstrate a relationship between the encephalomyelitis and the presence of antibodies. Thomas and associates [12] studied the role of a circulating antibody in the production of encephalitis in dogs following immunization with homologous brain extract. Frick [4] studied antibody formation after injection of homologous and heterologous brain tissue. Ferraro and Jervis [6] produced demyelination of the central nervous system in monkeys by intramuscular injections of aqueous solutions and alcohol-ether extracts of normal rabbit brain. Morgan ‡ induced allergic encephalomyelitis in monkeys by injecting normal monkey cord and normal monkey brain tissue. According to Ferraro,[15] the pathologic process of demyelinating diseases can be explained on the basis of allergy. This interpretation of the pathologic changes in demyelinating disease as an allergic reaction does not exclude the histogenesis of plaques through thrombus formation, as reported by Putnam.§ In his study of vascular changes in experimental anaphylaxis, Ferraro [18] described the inflammatory changes in the course of reaction, which he found to be similar to those found in the central nervous system in demyelinating diseases, leading to a conclusion that all these changes were due to allergic reaction. Jervis and Kaprowski [19] have produced encephalomyelitis in a guinea pig by injections of brain antigens with adjuvants. They interpreted this encephalomyelitis as an allergic condition due to antigen-antibody reaction with in the central nervous system. In their "Experimental Studies in Allergic Encephalomyelitis," Ferraro, Roizin, and Cazzulo [20] have emphasized again that the histological process, characterized principally by vascular and inflammatory reactions, may be due to immunological reactions of the allergic type.

The technical part of this work was done by Dr. Galina Rakoczy.

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* References 3 and 4.

† References 5 through 8.

‡ References 13 and 14.

§ References 16 and 17.

Recently Olitzky and Tal [21] produced acute disseminated encephalomyelitis in mice by injections of Folch-Lees proteolipide fractions A, B, and C, and Waksman and Morrison [22] demonstrated weakly positive skin reactions with these fractions in rabbits in which experimental encephalomyelitis was induced by injections of homologous spinal cord tissues. This impressive work, reviewed at length by Schumacher,[23] leads one to suppose by analogy that multiple sclerosis may also be a condition arising on an allergic basis and that the sera of multiple sclerosis patients may contain antibrain antibodies. The antigen in the case of multiple sclerosis is unknown—it may be either brain tissue or some other constituent of the nerve tissue, as was questioned by Lumsden and associates,[24] or autoantigen derived from the patient's own nervous system after an initial trauma or stimulation; hence, our decision to perform the complement fixation tests with the antigens prepared from the brains of multiple sclerosis patients.

Many antigens were tried and found wanting. Much time and effort was spent in doing tests with three sets of proteolipides A, B, and C, each set prepared, respectively, from a multiple sclerosis brain, a normal brain, and the brain of a schizophrenic. Dr. Marjorie Lees, of the McLean Hospital Research Laboratory, had prepared these sets for us. The alcoholic extracts of three multiple sclerosis brains and one alcoholic extract of a normal, non-multiple-sclerosis brain were used as antigens, making in sum six antigens used in diagnostic tests and one from a normal brain for the control test. Our wishful expectations for a specific diagnostic test with these antigens did not materialize, but in the course of this work several observations worthy of recording were made and are here reported.

MATERIALS AND METHODS

The usual technique of complement fixation test was used. The serum under investigation was inactivated at 56 C for one-half hour. The antigens were freshly prepared and used in appropriate dilutions after the tests for anticomplementary reaction. All sera were tested for autofixation. Tubes containing 0.25 cc. each of antigen, patient's inactivated blood serum, and complement were incubated for 45 minutes at 37 C. Fifteen minutes later the hemolytic system, prepared by mixing well-washed sheep cells with amboceptor, was put there also for 30 minutes. Both systems being ready for test at the same time, 0.5 cc. of sensitized hemolytic system was added to each tube of the first system and the tubes returned to the incubator for another hour. Preliminary readings were taken and the tubes left overnight at the room temperature in winter and in the refrigerator in summer, and the final readings taken. The serum of the patient was used in dilution of 1:5 in the saline; antigens 1, 2, and 3 were used in dilutions of 1:50, and antigens 4, 5, and 6 in 1:4 and 1:5 dilutions. Two units of complement and hemolytic system three times as strong as its titer were used in this test. Sheep cells were washed many times and then diluted with saline to make a 3% solution. The proteolipides were the first substances used as antigens. They were very difficult to force into solution, as they first had to be dissolved in chloroform and methyl alcohol. With trial and error, these fractions were dissolved, diluted, and used as antigens. Eleven antigens were prepared from these proteolipides and tried with a large number of sera. All tests gave negative results, except the tests with one fraction. This fraction, acetone supernatant containing about 85% of cholesterol, represents the stage preceding the final extraction of proteolipide C. These acetone-soluble fractions, prepared from a multiple sclerosis brain, a normal brain, and the brain of a schizophrenic, were dissolved in 95% alcohol, diluted with saline to make a 3% solution, and used as antigens 1, 2, and 3. Some positive and some negative results were obtained with these antigens, both with multiple sclerosis and with normal sera. The results speak either against the specificity of this antigen in multiple sclerosis or suggest that the presence of these antibodies is not related to the destruction of myelin. The alcoholic extracts of three multiple sclerosis brains and one normal brain were prepared by us in a following manner: Pieces of the brain fixed in 10% formalin were cleaned of meninges and blood vessels and washed in tap water for 8 to 10 days, dried with filter paper, and finely ground. The brain was emulsified in alcohol, in a proportion of 1 gm. of brain tissue to 5 cc. of alcohol, and stored for 10 days at room temperature, shaken several times a day, filtered through the paper, diluted four or five times with saline, and used as antigens. These are the antigens 4, 5, and 6. The sera of each patient and of the controls were tested with all three antigens and with the control antigen prepared from a normal brain. The strengths of these reactions were marked from 0 to 4+. It was noticed that the same sera reacted differently to these antigens, giving the impression that the antigens prepared under identi-

TABLE 1.—*Reactions of Sixty Multiple Sclerosis Sera to Two Types of Multiple Sclerosis Antigens*

Patient		Acetone-Soluble Fraction			Alcoholic Extract of M.S. Brain					
					No. 4		No. 5		No. 6	
		No. 1 1:50	No. 2 1:50	No. 3 1:50	1:4	1:5	1:4	1:5	1:4	1:5
1	C. S.	−	−	−	−	−	−	−	−	−
2	H. C.	++++	+++	++++	++++	++++	++++	+++	+++	++
3	E. L.	++	+	++	++++	++	++	−	+++	+
4	F. C.	++	+	++	+++	+	+	−	++++	++
5	J. B.	−	−	−	−	−	−	−	−	−
6	P. D.	−	−	−	−	−	−	−	−	−
7	M. M.	++	−	+	++++	+++	++	−	+++	−
8	E. S.	−	−	−	−	−	−	−	−	−
9	E. O.	−	−	−	+++	++	−	−	++	−
10	A. K.	−	−	−	−	−	−	−	−	−
11	J. C.	+	−	+	++++	++	+	−	+++	++
12	L. F.	−	−	−	−	−	−	−	−	−
13	A. M. O'D.	++	−	++	++++	+++	++	+	+++	++
14	M. Z.	++	+	++	++++	+++	++	++	++++	+++
15	H. S.	−	−	−	−	−	−	−	−	−
16	J. H.	−	−	−	++	−	+	−	−	−
17	E. J.	++++	++++	++++	++++	++++	++++	++++	++++	++++
18	E. D.	−	−	−	++	+	−	−	+	+
19	M. C.	−	−	−	−	−	−	−	−	−
20	S. P.	−	−	−	++++	+	++++	++	++	−
21	V. R.	−	−	−	+++	+++	++	+	+	+
22	A. H.	−	−	−	+++	+++	++++	+++	++	++
23	R. M.	−	−	−	++++	++	−	−	++	−
24	G. McN.	++	−	+++	+++	+	−	−	+	−
25	E. A.	−	+	+	+++	++	−	−	+	−
26	H. R.	++++	++++	++++	++++	++	−	−	++	+
27	J. C.	−	−	−	+++	+	−	−	+	−
28	K. Q.	+++	++	+++	++++	+++	−	−	++	+
29	P. P.	+++	++	++++	++++	++++	++++	+++	++++	+++
30	R. D.	−	+	++	+++	−	+++	−	+++	+
31	E. P.	+	+	++++	++++	++	++++	++++	++++	+++
32	W. F.	−	−	−	−	−	−	−	−	−
33	M. O'C.	+++	++	++++	+++	−	+++	−	++++	+
34	Ch. L.	−	−	−	−	−	−	−	++	−
35	R. G.	−	−	−	++++	−	+	−	−	−
36	P. S.	−	−	−	++++	−	+++	−	−	−
37	R. McD.	++	+	++	++++	++++	++++	+++	+++	−
38	J. G. H.	−	−	−	+++	+	+	−	−	−
39	M. D.	−	−	−	+++	+	−	−	+	−
40	M. H.	−	−	−	−	−	−	−	+	−
41	M. M.	−	−	+	+++	+	−	−	+	−
42	A. N.	−	−	−	++	−	−	−	+	−
43	A. B.	−	−	++	++++	++++	++++	++++	+++	+
44	Dr. T. B.	−	−	−	++++	+++	−	−	−	−
45	E. F.	−	−	−	−	−	−	−	−	−
46	C. B. E.	+	−	++	++++	+++	−	−	+	−
47	D. B.	−	−	−	++++	+++	++	+	+	+
48	E. N.	+++	++	++++	++++	++++	−	−	−	−
49	J. C.	−	−	+	++++	+++	−	−	−	−
50	M. D.	−	−	+	++++	+++	−	−	+	−
51	M. D. L.	++	+	++++	++++	++++	++	+	++	+
52	M. S.	++	+	+++	++++	++++	+	+	+	+
53	H. B.	+	+	++	++++	++++	++++	+++	+++	++
54	H. H.	−	−	−	+	−	−	−	+	−
55	M. R. D.	++	+	+++	++++	++++	++++	+++	+++	++
56	N. W.	−	−	−	−	−	−	−	++	−
57	T. d'A.	−	−	−	−	−	−	−	−	−
58	W. K.	−	−	−	−	−	−	−	−	−
59	A. N.	++	+	++	++	−	+	−	++	−
60	G. F.	−	−	−	+	−	−	−	−	−

TABLE 2.—*Reactions of Sixty Multiple Sclerosis Sera to Two Types of Multiple Sclerosis Antigens*

	Patient	Acetone-Soluble Fraction			Alcoholic Extract of M. S. Brain		
		No. 1 1:50	No. 2 1:50	No. 3 1:50	No. 4 1:4	No. 5 1:4	No. 6 1:4
61	H. C.	−	−	−	−	−	−
62	Miss A. M.	++++	++++	++++	++++	++++	+++
63	M. C.	++	++	+++	++	+	+
64	C. O.	+	+	+++	++	+++	+++
65	P. G.	++	++	+++	+++	+++	+++
66	P. G.	++	++	+++	+++	+++	++
67	Dr. R. B.	++	+	++	+++	+++	+++
68	H. McD.	+	−	−	−	+	−
69	E. C.	+	−	+	+	−	−
70	P. L.	+	−	+	+	+	++
71	M. J. B.	+	−	+	++	+	++
72	T. D.	−	−	++	+	+	−
73	C. I.	++	−	+++	+++	+	++
74	M. G.	+	+	+	+	−	+
75	M. C.	++	−	+++	+++	−	+
76	P. C.	−	−	−	+	+	+
77	L. K.	−	−	−	+++	+++	+++
78	A. P.	+	+	+	+++	+++	++
79	G. F.	−	−	−	+	++	++
80	L. G.	+	+	+	++++	++++	+++
81	T. S.	+	−	−	+++	+++	+++
82	F. D.	+	−	+	++++	+++	+++
83	P. O.	++++	++	+++	++++	++++	+++
84	T. J.	−	−	−	++++	+	+
85	M. K.	++	+	++	+	+	+
86	A. P.	++	−	++	++	++	+
87	M. M.	+	−	−	++++	++++	++++
88	P. M.	−	−	−	++	++	++
89	L. W.	+++	+	+++	++++	++++	++
90	E. R.	++	−	−	+	++	+
91	F. M.	−	−	−	+	±	+
92	P. D.	−	−	−	+++	+++	+++
93	W. S.	+++	++	+++	++	++	++
94	M. T.	−	−	−	++	++	++
95	B. C.	+	−	++	++++	++++	++++
96	F. T.	+++	++	++	+++	+++	+++
97	B. B.	++++	++++	++++	++++	++++	++++
98	F. R. G.	+++	++	+++	++++	++++	++++
99	F. G. S.	+++	++	+++	++++	++++	++++
100	L. W.	+++	++	+++	++	++	++
101	T. L.	−	−	−	+	±	±
102	D. H.	+	+	+	++	++	++
103	G. M.	−	−	−	−	−	−
104	A. M.	++	++	++	++++	++++	++++
105	H. L.	−	−	−	++	++	++
106	G. K.	+	+	++	++++	++++	++++
107	E. J.	−	−	−	+	+	+
108	L. S.	−	−	−	−	−	−
109	M. M.	−	−	−	++++	++++	++++
110	F. A.	−	−	−	++	++	++
111	N. Z.	−	−	±	±	±	±
112	E. C.	±	+	+	+	++	++
113	M. F.	−	−	−	−	−	−
114	A. L.	−	−	−	−	−	−
115	G. T.	−	−	−	−	−	−
116	D. La R.	++	++	++	++++	+++	+++
117	M. M.	−	−	−	−	−	−
118	R. A. M.	++++	++++	++++	++++	++++	++++
119	R. Z.	−	−	−	−	−	−
120	J. F.	−	−	−	+	+	+

TABLE 3.—*Reactions of Control Sera to Multiple Sclerosis Brain Antigens*

Control Normal Blood		No. 1 1:50	No. 2 1:50	No. 3 1:50	No. 4 1:4	No. 5 1:4	No. 6 1:4
1	L. V.	++++	++++	++++	−	−	+
2	N. S.	−	−	−	++	−	+
3	Dr. V. S.	−	−	−	−	−	−
4	Dr. W. H.	−	−	−	−	−	−
5	Dr. D. S.	−	−	−	−	−	−
6	Dr. M. B.	−	−	−	−	−	−
7	C. Y.	++++	++++	++++	++	−	−
8	J. S.	−	−	−	−	−	−
9	Dr. W. T.	++++	++++	++++	−	−	−
10	Dr. R. N.	−	−	−	−	−	−
11	Dr. R. J.	−	−	−	−	−	−
12	Rev. R. L.	++++	++++	++++	−	−	−
13	Dr. J. A.	−	−	−	−	−	−
14	Dr. P. P.	−	−	−	++	−	−
15	P. T.	−	−	−	−	−	−
16	Dr. N. R.	..	..	..	..	..	..
17	Dr. J. P.	++++	++++	++++	++++	++++	+
18	Dr. G. G.	−	−	−	−	−	−
19	Dr. L. D.	−	−	−	+++	+++	+
20	J. O. D.	−	−	−	++	+	−
21	Dr. J. M. M.	−	−	−	−	−	−
22	Dr. W. P.	++++	++++	++++	++++	++++	+++
23	Dr. I. R.	−	−	−	+++	+++	+++
24	S. D.	−	−	−	−	−	−
25	G. W.	−	−	−	−	−	−
26	D. D.	−	−	−	−	−	−
27	W. B.	−	−	−	+	+	+
28	W. N.	−	−	+	+	+	+
29	W. C.	−	−	−	−	−	−
30	J. R.	++++	+	++++	++++	++++	++++
31	Dr. Z. L.	−	−	−	−	−	−
32	Dr. S. C.	++	+	++	+++	+++	++
33	L. G.	++	+	++	+++	++	+
34	Dr. F. W.	Anti	−		Complementary		
35	Dr. A.	−	−	−	−	−	−
36	J. O.	−	−	−	−	−	−
37	M. L.	++	++	++	+++	+++	+++
38	B. B.	++	−	+	+	+	+
39	W. G. R.	++	++	++	++	++	++
40	R. V.	−	−	−	−	−	−
41	M. G. D.	−	−	−	−	−	−
42	D.	+	−	+	−	−	−
43	C. B. R.	−	−	−	−	−	−
44	Mr. G.	−	−	−	−	−	−
45	M.	−	−	−	−	−	−
46	A. M.	−	−	−	−	−	−
47	G. O. B.	+++	++	+++	++	+++	+++
48	G.	−	−	−	−	−	−
49	Miss A.	−	−	−	−	−	−
50	J.	+	−	−	+	−	++
51	Miss D. S.	++	−	−	+++	+++	+++
52	L. S.	−	−	−	−	−	−
53	A. H.	−	−	−	−	−	−
54	G. A.	−	−	−	−	−	−
55	F. S.	−	−	−	−	−	−
56	F. J.	−	−	−	−	−	−
57	P. L.	−	−	−	−	−	−
58	F. G.	−	−	−	−	−	−
59	J. P.	−	−	−	−	−	−
60	Mr. X.	−	−	−	−	−	−

cal conditions were of different strength. More and stronger reactions were seen with antigen 4 than with the other two. More positive reactions were given by these sera with the alcoholic extracts of the brain tissue than with the acetone supernatant (Tables 1, 2, and 3).

RESULTS

When the findings with these antigens in 120 multiple sclerosis patients were tabulated, multiple sclerosis sera with all six antigens were 83.3%, and the positive tests in control groups (normal, arteriosclerotic, and syphilitic patients) were 42.6%, showing the difference of 40.7%, which is significant beyond the 0.01 level of probability (Table 3). When the multiple sclerosis sera were tested with the antigen prepared from a non-multiple-sclerosis, normal brain, they gave 11.7%

TABLE 4.—*Number and Percentage of Positive Tests in All Groups*

	0	1	2	3	4	5	6	Total	%
Multiple sclerosis patients	20	5	13	22	10	13	37	120	83.3
Normals	37	1	3	5	4	1	9	60	38.33
Arteriosclerotics	11	4	—	3	—	1	1	20	45.0
Syphilitics	10	1	1	3	4	1	1	21	52.4

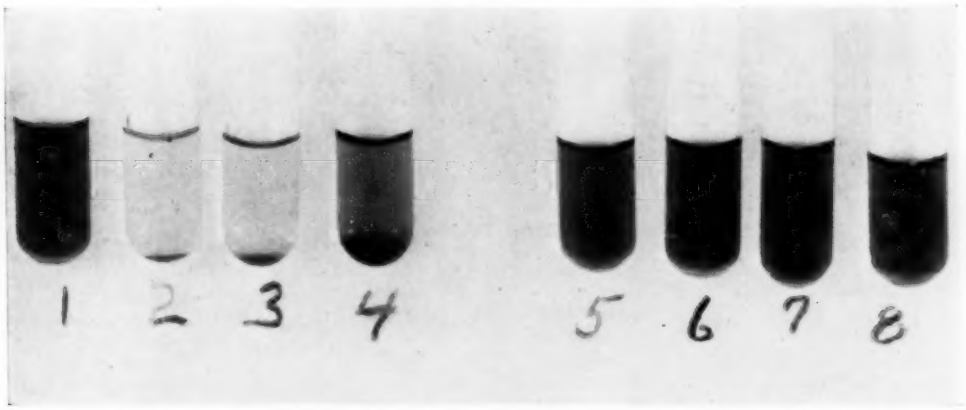
TABLE 5.—*Reactions of Multiple Sclerosis and Normal Sera to Alcoholic Solution of Cholesterol*

M.S.		Antigens: Saturated Alcoholic Solution of Cholesterol 1:50	Antigens: Normal Brain
8	E. S.	—	—
15	H. S.	—	—
22	A. H.	+	—
33	M. O'C.	+	—
43	A. B.	—	—
51	M. DiL.	++	+
52	M. S.	—	—
53	H. B.	—	—
55	M. R. D.	—	—
62	A. M.	—	—
63	M. C.	—	—
64	C. O.	—	—
65	P. G.	+	—
66	P. G.	—	—
68	H. McD.	—	—
69	E. C.	—	—
70	P. L.	—	—
71	M. J. B.	—	—
73	C. I.	—	—
74	M. G.	—	—
75	M. C.	—	—
80	L. G.	—	—
81	T. S.	—	—
82	F. D.	—	—
83	P. O.	+	±
84	T. D.	—	—
85	M. K.	—	—
86	A. P.	+	±
87	M. M.	±	—
88	P. M.	—	—
89	L. W.	+	—
90	E. R.	—	—
91	F. M.	—	—
92	P. D.	—	—
93	Wm. S.	±	—
94	M. T.	—	—
95	B. C.	—	—
96	F. T.	—	—
98	F. R. G.	+	+
99	F. S.	+	+
100	L. W.	—	—
101	T. L.	—	—
102	D. H.	—	—
103	G. M.	—	—
104	A. M.	—	—
105	H. L.	—	—
106	G. K.	—	+
107	E. J.	—	—
108	L. S.	—	—
109	M. M.	—	—
110	F. A.	—	—
111	N. Z.	—	—
112	E. C.	—	—
113	M. F.	—	—
114	A. L.	—	—
115	G. T.	—	—
116	D. LaR.	+	+
117	M. M.	—	—
119	R. Z.	—	—
120	J. F.	—	—

it appeared that, as far as the complement fixation tests are concerned, the difference between the multiple sclerosis and the normal sera is one of a degree, but the difference is significant enough to make this test statistically valid. The positive findings in positive and 83.3% negative reactions. When tested with a saturated alcoholic solution of pure cholesterol diluted 1:50 for comparison with the first three antigens, the same sera gave 20.0% positive and 80.0% negative reactions (Table 5). The figure for positive

tests with both control antigens was 21.66% (Table 4). The difference between 83.3% of positive tests with multiple sclerosis antigens and 21.66% positive reactions in the same sera with the control antigens is 61.64%, which is statistically valid. We have compared our findings with those reported by Sachs and Steiner [1] and Steiner [2] and confirmed by Frick.[3] They obtained 42% positive reactions in 289 multiple sclerosis patients and 3% in the control group, which consisted of patients with suspected multiple sclerosis, other diseases of the central nervous system, and non-nervous-system diseases. They used one antigen in each case, while we used six. The response of the same sera to different antigens being varied, the total response in our cases was higher, but the difference in their cases between the multiple sclerosis sera and the normal controls was 39% and in our cases 40.7%, apparently a good agreement.

As another control, we have done complement fixation tests with the antigens prepared from (*a*) a normal brain, (*b*) pure cholesterol, and (*c*) multiple sclerosis brain on the sera of normal healthy young men. As was expected, the normal sera gave negative results with the first two antigens, but 36.6% of these normal sera gave positive reactions with multiple sclerosis brain antigens. Sachs and Steiner considered only those tests diagnostic which showed positive reactions with multiple sclerosis brain antigens and negative with antigens prepared from other brains. They do not mention normal brain antigens. We have found that very far-advanced, clinically severe cases may give completely negative reactions to all antigens, regardless of the age of the patient, an observation in agreement with Steiner's findings.[2] He found the highest percentage of positive reactions in younger age groups, the number of positive reactions decreasing



The complement fixation tests on the patient's serum before and after addition of normal blood.

Tube *1*, test for anticomplementary action of the multiple sclerosis blood serum with the hemolytic system and complement added, but without the antigen. Negative reaction.

Tube *2*, complement fixation test. Multiple sclerosis serum with antigen 4. Positive reaction.

Tube *3*, complement fixation test. Multiple sclerosis serum with antigen 5. Positive reaction.

Tube *4*, complement fixation test. Multiple sclerosis serum with antigen 6. Positive reaction.

Tube *5*, test for anticomplementary reaction of multiple sclerosis blood serum mixed with equal amount of normal blood serum, with the hemolytic system and complement, but without the antigen. Negative reaction.

Tube *6*, complement fixation test. Multiple sclerosis blood serum plus equal amount of normal blood serum plus antigen 4. Negative reaction.

Tube *7*, complement fixation test. Multiple sclerosis blood serum plus normal blood serum plus antigen 5. Negative reaction.

Tube *8*, complement fixation test. Multiple sclerosis blood serum plus normal blood serum plus antigen 6. Negative reaction.

TABLE 6.—*Reactions to Multiple Sclerosis Brain Antigens of Multiple Sclerosis Sera Mixed with Equal Amounts of Normal Sera*

	Multiple Sclerosis Sera Mixed with Equal Amounts of Normal Sera	Antigens 1 1:50	2 1:50	3 1:50	4 1:4	5 1:4	6 1:4
1	E. L.—m. s.	++	+	++	++++	++	+++
	E. L. and Dr. S.	−	−	−	−	−	−
	E. L. and S.	−	−	−	−	−	−
	E. L. and W. C.	−	−	−	−	−	−
	E. L. and G. W.	−	−	−	−	−	−
2	A. H.—m. s.	−	−	+	+++	++++	++
	A. H. and Dr. S.	−	−	−	+	+	−
	A. H. and S.	−	−	−	+	+	−
	A. H. and W. C.	−	−	−	+	+	−
	A. H. and G. W.	−	−	−	+	+	−
3	M. O'C.—m. s.	+++	++	++++	+++	+++	++++
	M. O'C. and Dr. S.	±	−	±	−	−	−
	M. O'C. and S.	−	−	−	−	−	−
	M. O'C. and W. C.	±	−	±	−	−	−
	M. O'C. and G. W.	±	−	±	+	−	+
4	D. B.—m. s.	−	−	−	++++	++	+
	D. B. and Dr. S.	−	−	−	−	−	−
	D. B. and D. D.	−	−	−	−	−	−
	D. B. and Dr. D.	−	−	−	−	−	−
	D. B. and G. W.	−	−	−	+	−	−
5	Mr. D.—m. s.	−	−	+	++++	−	+
	Mr. D. and Dr. Z. L.	−	−	−	−	−	−
	Mr. D. and D. D.	−	−	−	−	−	−
	Mr. D. and W. C.	−	−	−	−	−	−
	Mr. D. and G. W.	−	−	+	+	−	−
6	S. T.—m. s.	−	−	−	++++	++++	++
	S. T. and Dr. S.	−	−	−	+	+	−
	S. T. and D. D.	−	−	−	−	−	−
	S. T. and Dr. D.	−	−	−	−	−	−
	S. T. and G. W.	−	−	−	−	−	−
7	V. B.—m. s.	−	−	−	+++	++	+
	V. B. and Dr. S.	−	−	−	−	−	−
	V. B. and D. D.	−	−	−	−	−	−
	V. B. and Dr. D.	−	−	−	−	−	−
	V. B. and G. W.	−	−	−	−	−	−
8	R. S.—m. s.	−	−	−	++++	+++	−
	R. S. and Dr. S.	−	−	−	+	−	−
	R. S. and D. D.	−	−	−	−	−	−
	R. S. and Dr. D.	−	−	−	−	−	−
	R. S. and G. W.	−	−	−	−	−	−
9	Mrs. P.—m. s.	+	+	++++	++++	++++	++++
	Mrs. P. and Dr. S.	−	−	−	+	−	−
	Mrs. P. and S.	−	−	−	+	−	−
	Mrs. P. and W. C.	−	−	−	+	−	−
	Mrs. P. and G. W.	−	−	−	+	−	−
10	R. McD.—m. s.	++	+	++	+++	+++	+++
	R. McD. and Dr. S.	+	−	−	+	−	−
	R. McD. and D. D.	−	−	−	+	−	−
	R. McD. and W. C.	−	−	−	−	−	−
	R. McD. and G. W.	−	−	−	+	−	−

	Multiple Sclerosis Sera Mixed with Equal Amounts of Normal Sera	Antigens 1 1:50	2 1:50	3 1:50	4 1:4	5 1:4	6 1:4
11	E. N.—m. s.	+++	++	++++	++++	−	−
	E. N. and Dr. S.	−	−	−	−	−	−
	E. N. and D. D.	−	−	−	−	−	−
	E. N. and W. C.	−	−	−	−	−	−
	E. N. and G. W.	−	−	−	−	−	−
12	H. B.—m. s.	+	+	++	++++	++++	+++
	H. B. and Dr. S.	−	−	−	−	−	−
	H. B. and D. D.	−	−	−	−	−	−
	H. B. and W. C.	−	−	−	+	−	−
	H. B. and G. W.	−	−	−	+	+	+
13	A. N.—m. s.	++	+	++	++	+	++
	A. N. and Dr. S.	−	−	−	−	−	−
	A. N. and D. D.	−	−	−	−	−	−
	A. N. and W. C.	−	+	−	+	−	+
	A. N. and G. W.	−	−	−	−	−	−
14	R. D.—m. s.	−	±	++	+++	+++	+++
	R. D. and Dr. Z. L.	−	±	+	+	−	−
	R. D. and D. D.	−	−	−	−	−	−
	R. D. and W. C.	−	−	+	+	−	−
	R. D. and G. W.	−	−	−	−	−	−
15	A. B.—m. s.	−	−	++	++++	++++	+++
	A. B. and Dr. Z. L.	−	−	+	++	−	−
	A. B. and D. D.	−	−	−	−	−	−
	A. B. and W. C.	−	−	+	++	+	−
	A. B. and G. W.	−	−	−	−	−	−
16	J. C.—m. s.	−	−	+	++++	−	−
	J. C. and Dr. Z. L.	−	−	−	−	−	−
	J. C. and D. D.	−	−	−	−	−	−
	J. C. and W. C.	−	−	−	−	−	−
	J. C. and G. W.	−	−	+	+	−	−
17	M. C.—m. s.	++	++	+++	++	+	+
	M. C. and Dr. J.	−	−	−	−	−	−
	M. C. and Dr. A.	−	−	−	−	−	−
	M. C. and G. W.	−	−	−	−	−	−
	M. C. and Dr. S.	−	−	−	−	−	−
18	C. O.—m. s.	+	+	++	++	+++	+++
	C. O. and Dr. J.	−	−	−	−	−	−
	C. O. and Dr. A.	−	−	−	−	−	−
	C. O. and G. W.	−	−	−	−	−	−
	C. O. and Dr. S.	−	−	−	−	−	−
19	P. G.—m. s.	++	++	+++	+++	+++	+++
	P. G. and Dr. J.	−	−	−	−	−	−
	P. G. and Dr. A.	−	−	−	−	−	−
	P. G. and G. W.	−	−	−	−	−	−
	P. G. and Dr. S.	−	−	−	−	−	−
20	P. G.—m. s.	++	++	+++	+++	+++	++
	P. G. and Dr. J.	+	−	+	+	+	−
	P. G. and Dr. A.	−	−	−	−	−	−
	P. G. and G. W.	+	−	+	+	−	−
	P. G. and J. Q.	−	−	−	−	−	−

in the fifth and sixth decades. Our results are not in complete agreement with this finding. Our youngest patient was a 19-year-old youth who had been sick for three years, and our oldest, a 72-year-old woman who had been sick for 33 years. His complement fixation test, done after three years of illness, was very strong, and hers, done after 33 years, very weak; but the similarity ends here. The largest number of our patients were in the fourth and fifth decades of life, and the tests were done 1 to 33 years after the appearance of first symptoms. In several cases the tests were repeated two or three times during either exacerbation or remission of the clinical symptoms. In no case did the positive test become completely negative during the improvement, although the strength of the complement fixation test noticeably decreased, from 4+ to 3+ or 2+, and even 1+. It seems that the age of the patient, the number of years of the duration of the illness, and the acuteness or chronicity of this condition are not reflected in the test. Some of our severest cases of long duration gave either weak or negative reactions. When we have mixed the serum of a multiple sclerosis patient giving a very strongly positive reaction with an equal amount of a normal serum giving a negative reaction with the same antigen, inactivated this mixture, and repeated the test, we have noticed that the positive reaction of the multiple sclerosis serum became negative (Figure). We have repeated this test with hundreds of multiple sclerosis sera and have noted the difference in the degree of this change, so that the results may be divided into two groups: The first, and larger, of the two consists of the sera that have become completely nega-

TABLE 7.—*Reactions to Multiple Sclerosis Brain Antigens of Normal Positive Sera Mixed with Normal Negative Sera*

	Controls	Antigens					
	Normal Positive Sera Mixed with Normal Negative Sera	1 1:50	2 1:50	3 1:50	4 1:4	5 1:4	6 1:4
1	J. R.	+++	+	++	++++	++++	++++
	J. R. and D.	+++	+	++	+++	+++	++
	J. R. and H.	+++	+	++	++++	++++	+++
	J. R. and W.	+++	+	++	++++	++++	+++
	J. R. and Dr. J.	+++	+	++	++++	++++	+++
2	W. P.	++++	+++	++++	++++	++++	++++
	W. P. and Dr. S.	++++	+++	++++	+	+	+
	W. P. and H.	++++	+++	++++	+	+	+
	W. P. and W.	++++	+++	++++	+	+	+
	W. P. and Dr. J.	++++	+++	++++	+	+	+
3	L. G.	++++	++	+++	++++	++	+
	L. G. and Dr. G. W.	++++	++	+++	++	+	+
	L. G. and S.	+++	++	+++	+	−	−
	L. G. and G.	+++	++	+++	+	+	−
	L. G. and R. V.	+++	++	+++	++	+	−
4	S. C.	++	+	++	++++	++++	++++
	S. C. and F. G.	+	+	+	++++	++++	+++
	S. C. and J. P.	++	+	++	++++	++++	+++
	S. C. and D.	++	+	++	++++	++++	+++
	S. C. and F. C.	++	+	++	++++	++++	+++
5	J. P.	++++	++++	++++	++++	++++	+
	J. P. and Dr. W.	++++	+++	++++	++	++	+
	J. P. and S.	++++	+++	++++	+++	++	+
	J. P. and G.	++++	+++	++++	++	+	+
	J. P. and R. V.	++++	++++	++++	+++	+	+
6	M. N.	++	++	++	++	++	++
	M. N. and Dr. W.	+	+	++	++	++	++
	M. N. and S.	+	+	++	++	++	++
	M. N. and G.	−	++	+	++	++	+
	M. N. and R. V.	+	++	++	++	++	+

tive, and the second, of those that have given a considerably weaker, but still a positive, reaction (Table 6). Only one multiple sclerosis serum did not change its original strongly positive reaction, although this serum was mixed with 11 different normal sera. All others showed indubitable change. When the normal blood sera of the control group which had given positive reactions with the multiple sclerosis brain antigens were mixed with normal negative sera, a great majority of these did not change their reactions from positive to negative, although some did show the decrease in intensity of the reaction (Table 7). These observations of the changes in the reaction in vitro led us to postulate that this phenomenon may be due to addition of the proteins present in normal sera and that the differences in amounts of proteins in normal sera may account for the difference in degree of the change of the reaction. The impression was that the addition of normal sera neutralized the complement-fixing bodies in the multiple sclerosis sera, liberating the complement.

It occurred to us that if this phenomenon observed in vitro should take place in vivo the patient might benefit from a transfusion with the blood of the donors selected on the basis of this test. Accordingly, we began transfusing our multiple sclerosis patients with the blood of the donors whose serum had changed the patient's serum from a positive to a negative one in vitro. So far, the number of the patients treated does not warrant definite conclusions, but the results are encouraging. The patients are given one blood transfusion a week for six consecutive weeks. If the hematocrit reading becomes high, the patients are transfused with the blood plasma from the donors similarly selected. The methods of treatment and the results are to be reported later.

SUMMARY AND CONCLUSIONS

The complement fixation tests with the solutions of Folch-Lees proteolipides A, B, and C, used as antigens, gave negative results.

The combined number of positive complement fixation tests with the multiple sclerosis brain antigens was 83.3% in multiple sclerosis patients.

The combined number of positive complement fixation tests in the control group was 42.6%.

The difference between the number of positive complement fixation tests in multiple sclerosis sera and the number of those in normal sera was 40.7%, a difference which is statistically valid.

The observation that the addition of normal sera to the positive multiple sclerosis sera reduces the positive reaction to a negative one, or to a much weaker one, led to a hypothesis that a substance is added capable of neutralizing the complement-fixing bodies, thereby liberating the complement.

This finding led to the selection of donors on the basis of this test for the treatment of the multiple sclerosis patients with blood transfusions.

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Psychologic Conflict and Electroencephalographic Patterns

Some Notes on the Problem of Correlating Changes in Paroxysmal Electroencephalographic Patterns with Psychologic Conflicts

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There have been a number of interesting reports in the medical literature which give data purporting to demonstrate a correlation between the occurrence or acute arousal of psychologic phenomena * and paroxysmal or deviant electroencephalographic activity of the type seen in epilepsy. Some investigators tend to emphasize the effect of psychologic activity on electroencephalographic activity.† Others tend to regard the psychologic activity as the affected variable and the electroencephalographic activity as the causal agent variable.‡ Psychologic activity (itself a concomitant of some kind of cortical and subcortical neurogenic processes) can possibly have either an inhibiting or a facilitating effect on the functioning of another region of the brain showing abnormal bioelectric discharges. At the same time, a region of abnormal bioelectrical discharge may suppress or facilitate neurogenic activity—and thus psychologic activity—in the same region or elsewhere in the central nervous system. Experimentally and clinically, it is a difficult problem to determine whether there is an effect of one type of cerebral phenomenon on another and to determine the nature of the effect.

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* For purposes of this discussion, the phrase "psychologic phenomena" is meant to include those processes of motivation, feeling state, and conflict which a person experiences and reports directly to another person, as well as those same processes which are inferred by observation of one person's behavior by another person.

† References 1 through 4.

‡ References 6, 7, and 9.

PURPOSE

This paper is a report of exploratory studies with selected epileptic patients attempting to determine to what extent psychologic activity can modify electroencephalographic activity of the type seen in epilepsy. It is hoped that this report will clarify some of the problems needing further research in this type of study.

PROCEDURE

Four epileptic patients were selected for these studies on the basis of their showing frequent (at least one every two minutes) clear-cut slow-wave, high-voltage paroxysms in their electroencephalograms. The reason for selecting this type of epileptic patient was that the effects on the abnormal electroencephalographic activity of introducing and withdrawing a psychologic activity could be observed directly on their electroencephalograms. The patients were male, between the ages of 20 and 35. One patient was studied intensively. The other three were studied more briefly and superficially.

REPORT OF A CASE

The following case material, of the patient studied most thoroughly, demonstrates some of the problems involved in correlating abnormal slow electroencephalographic patterns with psychologic conflicts.

CASE 1.—The patient was a 24-year-old Army private of Polish Catholic origin. There was no familial history of epilepsy. There was no history of recent trauma or infection. His first seizure occurred at the age of 23, when he was returning to his military post after a three-day leave. It was exceedingly important to him never to make a mistake, break rules, or provoke displeasure in persons

of authority. In the service of such strong deference and obedience to authority, he anxiously hurried back to his post and checked in several seconds before the "deadline." Fifteen minutes later he had his first epileptic seizure, a grand mal spell. He had another seizure two days later, and on the next day still another one.

On admission to the hospital he was agitated, very tense, and depressed. He had somatic symptoms involving every body system. Among other things, he complained of hypersalivation, of hearing difficulty, of disturbances of the sense of taste and smell. He said that he had episodes during which he felt "pins and needles" from the neck down, and during which he felt that he could not move his hands, wherever he put them—on his lap, on his chest, or so on. He had the persistent feeling he was doomed to die suddenly. (Not until several weeks after admission to the hospital could he tell of his dissatisfaction with military life and rebelliousness toward Army officers. The more he reported such feelings the less pronounced were his symptoms of depression and irrational fear of dying.)

Neurological and medical studies, including blood counts, urinalyses, cerebrospinal fluid studies, a glucose tolerance test, skull x-rays, and pneumoencephalogram, were all within normal limits. Repeated electroencephalographic studies revealed predominantly right temporal, frequent bursts of 3-cps high-voltage spike-and-wave activity (Fig. 1, *Case I*).

His seizures occurred three to four times per week during the first two months of hospitalization, although he was given diphenylhydantoin sodium and phenobarbital. Seizures were most frequently nocturnal and began to occur three to six times in rapid succession. Then they gradually decreased in frequency over the next month, and none occurred during the last two months of observation.

Personality studies revealed he was a perfectionistic, scrupulous, very religious young man. He was exceedingly dependent on his parents, obsessively preoccupied with the fear he might disappoint or hurt his mother. He emphasized that his mother taught him "the difference between right and

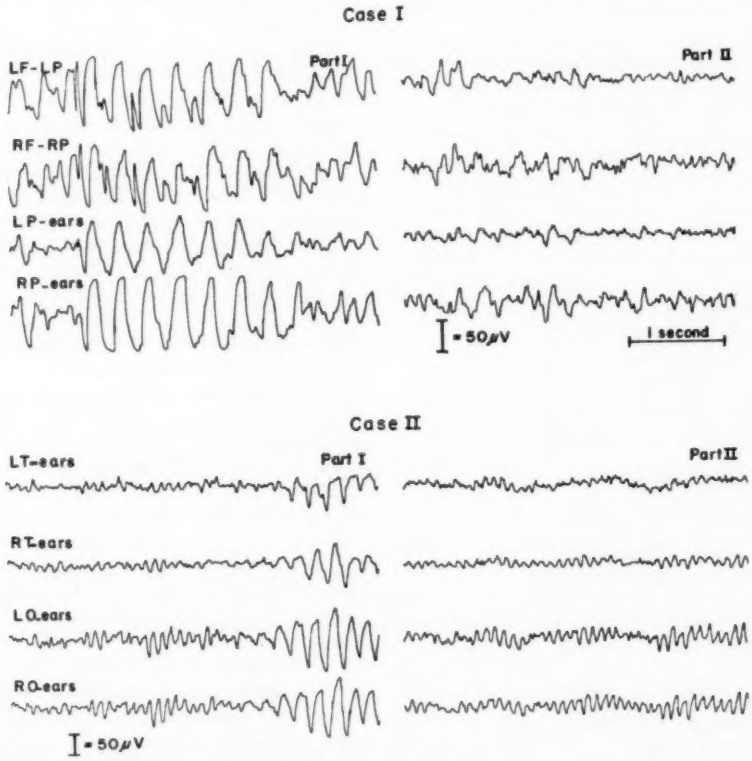

Fig. 1.—Electroencephalograms of two epileptics whose paroxysmal brain wave activity was suppressed completely (*Case II*) or markedly reduced (*Case I*) when they counted silently or talked to the examiner.

Part I: Patient resting with eyes closed.
Part II: Eyes closed and patient counting silently.

wrong," and he said that he became anxious when he did not live up to the standards she inculcated in him. He was boastful of what he considered his exemplary behavior—absolutely no smoking, no drinking, no sex—and he was scornful of soldiers more self-indulgent in these respects. His precollege occupational interests had been in becoming either a mortician or a clergyman, and these vocational interests well indicated his preoccupations and his preferred ways of relating with other people. He decided in favor of being a mortician and got trained in this vocation. He was operating a successful mortuary business before being drafted into military service.

During his hospitalization, lasting a period of five months, studies were made of psychologic factors associated with the occurrence of paroxysmal electroencephalographic patterns. He was interviewed during six electroencephalographic recordings, the interviews occurring in the middle period of each 45-60 minutes of recording, while he was resting supine with eyes closed.

The activity of talking with someone in itself was found to reduce significantly the frequency of paroxysms (greater than a duration of one second) of high-voltage slow activity in this patient (Table). The effect of other types of external and internal stimuli on the frequency of paroxysmal electroencephalographic activity was observed. Repeated external auditory stimuli—loud and startling sounds, noises, or music—had no effect whatsoever on the frequency of paroxysms. For instance, in one session a rate of 12.9 high-voltage slow-wave paroxysms occurred per 10 minutes during a period without loud or startling auditory stimuli, as compared with a rate per 10 minutes of 13.2 bursts of this sort during a period of minimal stimulation. He was not asleep during this time. Finger tapping by the subject during this same session reduced the frequency of the paroxysms to 9.2 per 10 minutes. Having the subject count silently by 3's eliminated the paroxysms completely for a period of 10 minutes.

Effect of a Patient's Talking (with the Investigator) on the Frequency of Paroxysmal High-Voltage Slow Activity (Case 1)

Date of Experimental Session	Number of Paroxysms (Greater Than One Second's Duration) of High-Voltage Slow Activity per 10 Minutes	
	During Conversation	During Absence of Conversation
Dec. 19	5.8	12.9
Jan. 2	4.2	20.5
Jan. 16	0.3	4.9
Feb. 6	0.0	1.0
Feb. 13	0.2	3.4
Feb. 20	0.3	0.9
	10.8	43.6

Since, in the instance of this subject, talking with his physician and doing, on request, silent simple arithmetic significantly "suppressed" the frequency of his slow-wave paroxysms, it was a problem to determine whether or not any specific emotional conflicts might either suppress or provoke abnormal cerebral electrical discharges. At no time did talking or silent counting increase the frequency of paroxysms beyond the rate they occurred when he was awake but silent. In order to determine the relationship of psychologic conflicts and the rate of electroencephalographic paroxysms in this patient, it was necessary to find out whether a transient release from the usual suppressor effect of verbal communication occurred at any specific times during the interviews. That is, were there to be found any common themes, conflicts, or situations, expressed in the patient's verbalizations or in the interactions of the patient and the interviewer, preceding the occurrence of a slow-wave burst in his electroencephalogram?

Study of electronic-tape-recorded interviews with this patient, synchronized with the electroencephalographic record, indicated that slow-wave paroxysms occurred roughly within 30 seconds after he expressed a fear of being criticized adversely or repudiated or after he criticized and repudiated himself. The thought of repudiation of himself by his mother and father, God, the Army, doctors, nurses, or the investigator appeared to be just as commonly followed by a slow-wave paroxysm. The effect of this psychologic state (presumably severe separation anxiety) appeared to eliminate transiently the suppressing effect of verbal communication on his abnormal electroencephalographic slow-wave bursts. Furthermore, actual adverse criticism of the patient by the investigator or another person was found to be followed by the slow paroxysmal cerebral electrical activity during certain recording sessions; no such paroxysmal activity occurred for 20 minutes of blander interviewing before and after such criticism.

Without any changes in anticonvulsant medication, the total frequency of this patient's paroxysms of cerebral dysrhythmia decreased over a period of two months, as can be seen in the Table, when the investigator attempted to mitigate the severity of the patient's very strict, inflexible conscience and help him feel acceptable and likable. And when the patient's self-criticism was not allayed, but abetted, the paroxysmal rate tended to increase (as in the session on Feb. 13). Concomitantly, with a decrease in the brief seizure patterns observed in the electroencephalograms, the patient's clinical status improved. No changes in

seizure frequency were observed after he was taken off anticonvulsant medication, during the third month of hospitalization.

RESULTS

Evidence that psychologic activity can influence the frequency of abnormal electroencephalographic activity is provided in this case study by the following data:

1. The observation of the suppressing effect of bland conversation, silent arithmetic, and, to a less extent, finger tapping on high-voltage slow electroencephalographic activity

2. The observation that the arousal of a psychologic state, such as severe separation anxiety, could transiently eliminate the suppressing effect of bland verbal communication and could release, through some unknown chain of intracerebral events, high-voltage slow-wave bursts

3. The observation that mitigation of the severity of this patient's strict and inflexible self-evaluation, through psychotherapy, was associated with a decrease in the rate of slow-wave paroxysms and a disappearance of frank seizures

These observations do not discount the likely possibility that seizure phenomena, and hence cerebral paroxysmal dysrhythmia, are caused by a complex of multiple factors, including genetic, traumatic, biochemical, and psychogenic. The influence of each factor in the complex of factors is probably different for each patient. In some persons psychologic phenomena may have no demonstrable effect on inciting or inhibiting seizure phenomena.

FURTHER OBSERVATIONS

To test this proposition further, three other young men patients with idiopathic epilepsy were studied. One of these patients had a familial history of epilepsy. Of the other two, one had the history of cerebral concussion, and the other had no familial or contributory history of cerebral injury to account for the epilepsy. Physical examination and clinical and laboratory diagnostic studies on these patients were essentially negative except for the electroencephalograms. After an initial psychiatric diagnostic evaluation, each patient was observed for two sessions during electroencephalographic recording. The effect was noted of silent counting, finger tapping, talking, and being questioned about emotionally sensitive topics. A brief summary of each patient's epileptic history follows.

CASE 2 (*Case II*, Fig. 1).—This patient was a 32-year-old man, whose seizures began at the age of 29. There was no familial history of epilepsy. Nor were there any infections, injuries, or illnesses that might presumably account for the development of his epilepsy. His seizures were initiated by a sensation of pressure in the ears, followed by tinnitus and a "feeling of dizziness," often relieved by lying down. Then he generally experienced a peculiar sensation of taste and smell and became mentally confused and disoriented. The spells occurred once or twice daily and lasted from 10 minutes to 2 hours. He and his family were aware of the development of a personality change since the onset of seizures, characterized by increased irritability, temper outbursts, and a feeling of increased inner tension. The patient reported that the arousal of his anger or fear could precipitate his epileptic episodes.

In the hospital environment, without medication, his seizures became infrequent. When he was put on phethenylate (Thiantoin) therapy, his seizures disappeared, but the personality features of irritability and hostile outbreaks persisted.

Four electroencephalograms, made on different occasions, showed no notable asymmetries or foci, no well-defined spikes during sleep, but runs of 12- to 16-cps sleep spindles, intermingled with slower waves of 3-4 cps. However, when he was awake, recurring high-amplitude 5- to 6-cps bursts appeared, and these were most prominent over the right temporal lobe.

Clinical Diagnosis.—Psychomotor epilepsy—acute brain syndrome of unknown cause.

CASE 3 (*Case III*, Fig. 2).—This patient was a 21-year-old soldier. His father had grand mal epilepsy for many years. The patient's seizures started at the age of 11. There was no aura or warning. He would suddenly lose consciousness, fall to the floor, and develop generalized symmetrical jerking movements, typical of grand mal. His seizures somehow stopped about the age of 14, and without the help of anticonvulsant medication he was seizure-free until the age of 21, after enlisting in the Army.

Upon hospitalization, and after getting diphenylhydantoin medication, his seizures were effectively controlled.

Electroencephalographic studies revealed recurring diffuse 3-cps high-voltage spike-and-wave patterns. Other diagnostic studies were negative.

Clinical Diagnosis.—Grand mal epilepsy—acute brain syndrome of unknown cause.

CASE 4 (*Case IV*, Fig. 2).—This 21-year-old man had no familial history of epilepsy. A year before the onset of his seizures, at the age of 20, he

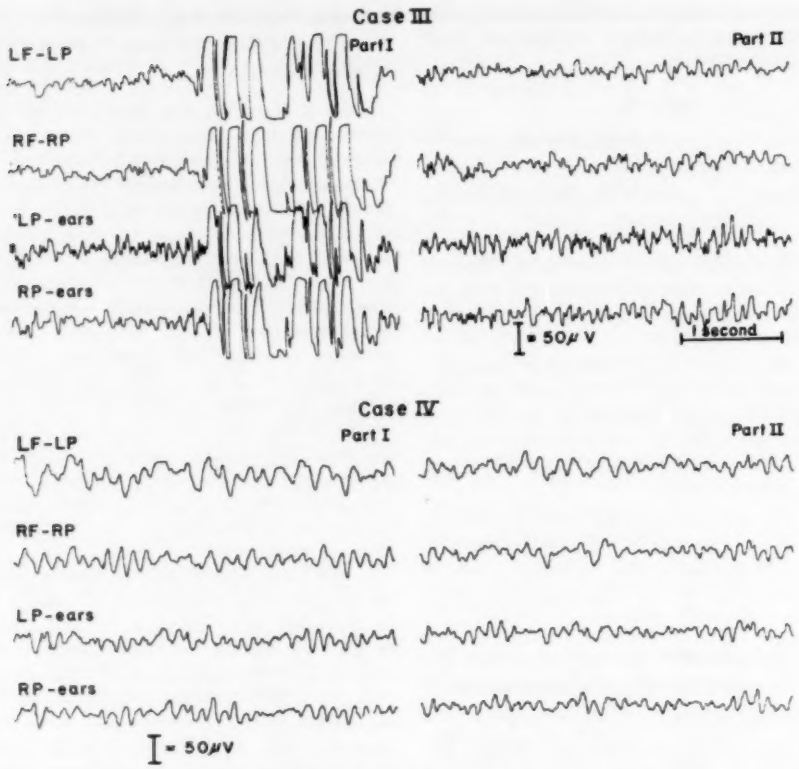

Fig. 2.—Electroencephalograms of two epileptics whose abnormal brain wave activity was only mildly suppressed (*Case III*) or essentially uninfluenced (*Case IV*) by silent counting or talking to the examiner.

Part I: Patient resting with eyes closed.
Part II: Eyes closed and patient counting silently.

was in an automobile accident, suffered a laceration of his left brow and cheek, and was unconscious for four days. For a while after this head injury he had severe headaches; these began to subside in frequency and intensity. Then suddenly he developed nocturnal grand mal seizures.

Initial electroencephalograms showed recurring 3- to 6-cps slow waves, primarily from the left frontal area, with similar but less prominent activity from the right frontal region.

During hospitalization the patient had no headaches or convulsive seizures. He was not on any anticonvulsant medication. Diagnostic studies were negative. Repeated electroencephalographic studies showed subsidence, and finally disappearance, of the brain wave abnormalities.

Clinical Diagnosis.—Grand mal epilepsy—acute brain syndrome associated with trauma.

FURTHER RESULTS

One of these patients (*Case IV*, Fig. 2) showed no change in the frequency of slow paroxysmal brain waves during these activities, as compared with periods of minimal activity. The other two patients showed a definite decrease in frequency of the slow high-voltage bursts, mostly during silent counting and while talking. There were insufficient data available in these case studies to determine whether the arousal of emotional conflicts during the recording of the electroencephalogram modified the frequency of abnormal electroencephalographic activity, although Case 2 volunteered that his actual seizures were often triggered, in his opinion, by situations in which he became angry or fearful. Of the two patients whose electroencephalograms were modifiable by the experimental activity, both the talking and the silent counting completely suppressed the paroxysmal slow rhythms in one patient

(Case 2), and in the other patient (Case 3) the conversing partially suppressed the slow-wave bursts and silent counting completely suppressed them. The inhibitory effect of talking and silent counting was more prominent in patients who presumably had a temporal lobe focus or a diencephalic focus and was less prominent in patients with a diffuse or frontal cortical slow dysrhythmia. The patient (Case 4) whose seizures began after suffering a brain concussion showed no changes in the frequency of slow brain waves while counting silently or talking.

COMMENT

There must be some structural and physiological mechanism that makes possible the inhibition of paroxysmal electroencephalographic patterns by such activities as talking, silently counting, tapping a finger, and so forth. Is an irritable focus of abnormal electrical bursts suppressed, when silent counting or talking is induced, because of the location of the irritable focus in relation to the neuronal units called into play by the talking or silent counting? And does such activity fail to inhibit the occurrence or spread of electrical discharges from an irritable focus because it involves neuronal discharges too remote from, and not directly enough connected to, the region of paroxysmal discharge? And are multiple irritable foci less susceptible to suppression by such means than single irritable foci?

This study cannot delineate the neurophysiological mechanisms by which activities such as talking or silent counting can have an inhibitory effect on the frequency of bursts of high-voltage slow waves. The tentative observation that the inhibitory effect was more prominent in patients who presumably had temporal lobe foci or a diencephalic focus suggests that the site of the irritable focus is important in determining whether slow electroencephalographic waves are suppressed by talking or silent counting. Evidence that rhythms other than 8½-12 per second coming from the temporal lobes in nonepileptics are modified by arithmetic problem solving has been demonstrated by Brazier.[5] She found that these rhythms became 180 degrees out of phase in the two temporal lobes during mental calculation, whereas alpha rhythms were 0 degrees out of phase. Such findings tend to support the idea that certain types of mental activity can modify certain types of localizations of abnormal (slow) waves. The neurologic mechanism which makes such phenomenon possible deserves investigation.

Why particular emotional content expressed verbally, such as fear of repudiation by the self or others, can counteract the suppressing effect of speech on abnormal brain rhythms is also not clear. It has been demonstrated in other studies, however, that resolution of the emotion conflicts of epileptic children by intensive psychotherapy can significantly reduce the seizure frequency of these children[8] Furthermore, external or internal threats to an epileptic's self-esteem and self-respect have been found to trigger epileptic seizures.§ What is not clear is the neurophysiological mechanism that makes such a phenomenon possible; this needs further study.

There is little question that epileptic seizure activity may cause disturbances in a person's subjective mental experiences. There is more question about a particular type and locus of abnormal electroencephalographic activity being responsible for all the observed disturbances in intellectual functioning and emotional expression in a patient. Gibbs and his co-workers[6] are inclined to conclude that all the peculiar behavioral manifestations or subjective reactions of an epileptic patient, particularly with anterior temporal lobe spikes, are a result of the unusual brain waves, or whatever causes such brain waves. To substantiate such a hypothesis, it would seem necessary to demonstrate that the behavioral or subjective reactions occur in conjunction with the abnormal electroencephalographic activity and do not occur when such electroencephalographic activity is absent. Even the interseі-

§ References 2, 4, and 8.

zure personality disorder of the patient with psychomotor epilepsy is attributed by Gibbs to disturbances in the temporal lobe.[6] Since the etiology of such a focal abnormality in the electroencephalograms of patients with psychomotor epilepsy in unknown, and since life stresses and emotional conflicts can precipitate many types of epileptic seizures, the investigation of the contribution such psychologic stresses may have in the precipitation of these seizures is warranted.

SUMMARY AND CONCLUSIONS

The extent to which certain psychologic activities and processes can modify electroencephalographic abnormalities of the kind seen in epilepsy was studied in four male epileptics between the ages of 20 to 35.

Doing silent mental arithmetic (counting by 3's) and the act of talking (regardless of content) either significantly reduced the frequency of abnormal, high-amplitude, slow-wave paroxysms or had no notable effect on the frequency. In no patient did such activities increase the frequency of these slow-wave bursts. The suppressing effect of doing simple mental arithmetic and of talking aloud was most pronounced in patients with temporal or presumably diencephalic foci; this observation should be checked on a larger series of patients.

In one epileptic patient, studied intensively, the spontaneous expression of specific emotional states—the wish for acceptance and love from an authority figure and a strong fear of repudiation—was regularly followed within 30 seconds by slow-wave, high-voltage activity. In this patient, the verbal expression of such emotionally charged ideas seemed to counteract the otherwise suppressing effect of speaking on such slow-wave electroencephalographic activity.

The structural and neurophysiological mechanism which makes possible the suppressing effect of doing mental arithmetic and of speaking on the paroxysmal slow-wave activity of some epileptics should be investigated further.

The triggering of epileptic-like activity in the electroencephalograms of certain epileptics by psychologic conflicts, and the elimination of such by psychotherapy, should be studied further, to improve both our knowledge of the pathogenesis of epileptic seizures and our skill in the therapeutic management of this condition.

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Intellectual and Affective Functions in Multiple Sclerosis

A Quantitative Study

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In 1943 Sugar and Nadell [1] reviewed the literature concerning mental changes associated with multiple sclerosis. Their survey disclosed considerable disagreement regarding the question of intellectual loss. They said:

> Charcot and Dupre referred to progressive dementia characterized by defects of memory, hallucinations, markedly expansive moods. . . . Hunt and Kraeplin were of the opinion that this disease was accompanied by slight mental changes, and that in a large number of cases those psychical alterations were merely transitory.

To our knowledge, estimates of intellectual impairment as a consequence of the disease, based upon clinical impressions, have varied from 2% (Cottrell and Wilson [2]) to 72% (Ombredane [3]). Although the procedure used by Ombredane did not provide a quantitative basis for group comparisons, he carefully studied 50 patients with multiple sclerosis and concluded that 36, or 72%, had very clear intellectual losses. He believed that the main loss was represented by difficulty in initiating mental effort toward the solution of problems and in the fatigability of mental functions, although he also observed losses in memory, association of ideas, and abstraction, in agreement with Seiffer [4] and Duge. [5] In consideration of the frequency and consistency with which he observed intellectual losses in multiple sclerosis, he said, "*Nous sommes donc autorisés à considérer le déficit des fonctions intellectuelles comme appartenant à la symptomatologie caractéristique de la sclérose en plaques.*" In 1921, however, the Association for Research in Nervous and Mental Disease concluded that mental deterioration was absent even when well-defined pathological changes in the brain were present.[6]

Except for the study by Brown and Davis,[7] it appears that only very recently have standardized psychological tests been used in studying this problem. Brown and Davis felt that changes in intelligence were possibly present, but they were unable to demonstrate them with their testing procedures. Burgemeister and Tallman [8] concluded that their results with the Rorschach test showed losses in organizing ability and abstraction similar to those shown in patients with definite brain damage. Canter (quoted by Harrower [9]) has summarized his findings * as follows:

> In multiple sclerosis, there appears to be an impairment of intellectual and emotional functions which can be objectively measured by means of psychological tests. . . . Generally the most striking psychological loss is inability to analyze and synthesize abstract problems.

Baldwin's [12] detailed investigation of the relationship of psychological test results to anamnestic and neurological findings in patients with multiple sclerosis revealed some intellectual loss in certain patients with multiple sclerosis but no loss in many others. She depended primarily upon the Hunt-Minnesota Test for Organic Brain Damage for assessing intellectual functions.† Other stud-

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Mrs. Barbara L. Melberg assisted with the test administration and statistical analysis.

* References 10 and 11.

† References 13 and 14.

ies ‡ have shown that this test not only misclassifies a large proportion of patients without brain damage, but also yields a high proportion of false-negative results. Baldwin notes reports of the evidence for failure in discrimination with the use of this test, and concludes that there was probably a greater difference in intellectual functioning between her control and multiple sclerosis groups than she was able to measure.

Although these recent results agree that intellectual impairment is present at least in a substantial proportion of patients with multiple sclerosis, the problem is complicated by the report of Diers and Brown.[17] These authors were unable to identify any quantitative indication of intellectual impairment in measurements made by the Wechsler-Bellevue Scale. The Wechsler-Bellevue Scale [18] is one of the most completely standardized and highly respected scales for adult intelligence presently in use. There is evidence to indicate, however, that tests of psychometric intelligence, or the Intelligence Quotient, is often not as sensitive to general intellectual losses caused by brain damage as are other procedures.§

Since both negative and positive conclusions regarding the question of intellectual loss in multiple sclerosis appear in the recent literature, it would seem that additional information is needed. The answer to the question is relevant to a thorough appreciation of the effects of multiple sclerosis and may be of particular value in anticipating the adjustive capacities and problem-solving abilities of patients with the disease.

CASE MATERIAL

In this study three groups of 13 patients each were used. One of the groups consisted of patients with multiple sclerosis; another, of patients with definite organic brain damage, and a third, of patients with no history or evidence of brain damage. In addition to careful classification within these groups, each patient was individually matched with a corresponding patient in the other groups on the basis of color, sex, age, number of years of formal education, and Wechsler-Bellevue full-scale Intelligence Quotient. Matching of the patients on the Wechsler-Bellevue I. Q. might be judged as too stringent a criterion in a study concerned with possible intellectual losses as a consequence of brain damage. While we realized the likelihood of minimizing the probability of obtaining intergroup differences with the tests used experimentally in this study, the procedure was followed in view of the report by Diers and Brown [17] of no identifiable loss in the Wechsler-Bellevue I. Q. in patients with multiple sclerosis. Since the variables which were matched might possibly influence the test results in ways not related to diagnosis, their influence was equated to permit greater confidence in attributing any experimentally obtained intergroup differences to multiple sclerosis or the presence or absence of brain damage. Such matching usually increases the reliability of intergroup differences in much the same way as would a substantial increase in sample size. The results in matching the groups on those variables with numerical value are shown in Table 1.

TABLE 1.—*Means and Standard Deviations on Equated Variables for Three Diagnostic Groups*

		Age	Education	I.Q.
Brain damage	Mean	34.15	10.54	92.53
	S.D.	8.46	2.44	17.78
Multiple sclerosis	Mean	33.61	11.46	93.61
	S.D.	6.70	2.17	20.79
No brain damage	Mean	33.54	11.77	94.38
	S.D.	8.33	2.45	17.55

The 13 patients with multiple sclerosis represented consecutive hospital admissions with this disease. There were 10 men and 3 women; all were white. Their ages at the time of this investigation ranged from 23 to 46 years. The illness had been present a few months in three patients and from 1 to 19 years in the remainder, giving a mean of 6.6 years. In all patients the symptoms and signs satisfied the usually accepted criteria for the diagnosis of this disease. Although evidence for the presence of disseminated lesions is required, there is often predominant involvement of some parts of the nervous system over others. Based upon clinical findings we have therefore roughly classified four patients as having predominant spinal cord involvement, two as having spinal-cerebellar symptomatology, two as showing predominantly cerebral involvement, and five as giving evidence of widespread dissemination of the lesions through the cerebrum, brain stem, cerebellum, and cord.

Eleven patients gave some indication by symptom or sign that the disease process was active in some part of the central nervous system at the time of investigation. In the remaining two the process had evidently been stationary a considerable time.

‡ References 15 and 16.

§ References 19 and 20.

In the clinical evaluation of the mental and emotional status there was no significant deviation from normal in seven patients. On the other hand, the six remaining exhibited defects in memory, judgment, abstraction, concentration, or emotional control.

Electroencephalograms were obtained on nine patients, six of whom showed normal tracings. Minimal abnormalities were found in two patients having widespread involvement and in one having predominant spinal-cerebellar dysfunction. The four on whom no test was done included two with disseminated symptomatology, one with predominant cerebral involvement, and one in whom the major symptoms and signs were referable to the spinal cord.

Of the 13 patients comprising the group with brain damage, pathology involving the cerebral cortex was corroborated at craniotomy in 10. This included glioma in four, cavernous hemangioma in one, subdural hematoma with cortical damage in two, and penetrating head injury with surgical débridement in three. The remaining three patients in this group gave either neurological or pneumoencephalographic evidence of brain damage. Although several of the patients were tested postoperatively, the tests were not administered until the patients had benefited maximally from hospitalization and were ready for discharge. Five of the postoperative patients had undergone surgery at other hospitals, seven months to several years before the present testing.

The 13 patients classified as having no damage to the brain was examined neurologically, and thorough histories relating to possible head injuries and neurological illnesses were taken. The examination and the history gave no indication of cerebral damage or dysfunction in any of them. Eight had neurotic illnesses of sufficient severity to cause them to seek psychiatric treatment. Of these, the diagnosis in six was "depression" and in two was "anxiety neurosis." The inclusion of a large proportion of depressed patients was deliberate, to counterbalance the possible slowness in reaction or lack of interest in the testing which might occur in the patients with multiple sclerosis or in those with brain damage. In a further effort to minimize the possibility of obtaining intergroup differences which could be attributed to circumstances other than diagnosis, five paraplegic patients were included to complete the group without brain damage. Three of these had spinal cord damage from trauma, although none had received a head injury or had ever been unconscious. Of the remaining two, one was paraplegic from a ruptured intervertebral disc, and the other, from a vertebral dislocation. The primary reason for including these patients was to help equate the group without brain damage and the other groups with respect to mobility handicaps, chronic illnesses, and frequent and extended hospitalizations. The paraplegic patients had been injured a mean of 3.8 years before they were tested in the present study.

All patients were cooperative when the tests were administered and seemed well motivated. The testing was presented as routine procedure, and the purpose was not explained.

PROCEDURE

A wide variety of psychological tests was individually administered, one and a half to two days being required for examination of each patient. The tests included the Minnesota Multiphasic Personality Inventory, Halstead's tests for measurement of biological intelligence, and the Rorschach Test.

Administration and scoring of the tests were done primarily by a person who had no knowledge of our plan for group comparisons. All tests were finally scored immediately after administration, and before any of the groups was composed. The present experimental design is aimed to provide evidence regarding the extent to which a sample of patients with multiple sclerosis resembled, in psychological respects, patients with brain damage and those with chronic illnesses not attributable to brain damage.

The tests were selected to obtain an adequate sampling of both intellectual and affective responses. The Minnesota Multiphasic Personality Inventory [21] has proved to be a useful screening device for detecting affective personality disturbances.‖ Halstead [19] has presented impressive evidence that his tests are sensitive to certain intellectual effects of organic cerebral cortical damage, particularly of the frontal lobes. The Rorschach Test has long been used for the evaluation of affective personality disturbances,¶ as well as psychological effects of brain damage.#

The tests provided quantitative results that permitted statistical analyses, which are presented below.

RESULTS

Minnesota Multiphasic Personality Inventory.—Although this test has been used rather extensively in both clinical practice and research, it may be appropriate to describe briefly its construction and purpose. The test consists of 550 statements, each printed upon a separate card. The statements refer to various aspects of the subject's feelings, symptoms, and behavior, including

‖ References 22 through 27.

¶ References 28 through 30.

References 31 through 37.

health, sexual adjustment, social attitudes, family life, general feeling tone, and interests. The subject is asked to sort the cards into True or False categories as they apply to him at the present time. Nine scales have been devised upon which the subject's responses are rated: Hypochondriasis, Depression, Hysteria, Psychopathic Deviate, Masculinity-Femininity (of interests), Paranoia, Psychasthenia, Schizophrenia, and Mania. These scales were developed on an entirely empirical basis through comparison of the answers given by carefully diagnosed psychiatric groups and a large group of normals, for example, answers differentiating the group of patients with the diagnosis of depression as contrasted with the normals contributed to the Depression scale. No a priori notions were used regarding how patients *should* answer the questions, but, rather, only the obtained results.

It is not customary to find a "high" score on only one scale in results on individual subjects. Generally, the entire profile is in the normal range, or two or more scales deviate significantly from the average, or "normal," range. Results obtained by Gough [27] indicate that the first three scales, Hypochondriasis, Depression, and Hysteria, typically are high for neurotics, and these have been called the "neurotic triad." The Psychasthenia, Schizophrenia, and Mania scales, in addition to the "neurotic triad," are usually high in psychotics.

The test also includes four so-called validating scales, three of which we have used. These are the ?, Lie, and F scales. The ? scale is a reflection of the number of items placed in a "Cannot Say" rather than a True or False category, and thus represents the number of items which the subject has dropped from consideration. The Lie scale is based upon items which most subjects would almost certainly have to answer truthfully in only one way, and represents the number of answers contradicting this general trend. The F scale comprises items which are answered in a certain way by all but a very small percentage of the general population. A high score on this scale indicates either inconsistency of responses through carelessness, uncooperativeness, or confusion, or deliberate answers by the subject to depict himself in an unfavorable light.

The values for the validating and diagnostic scales are given in T-scores, which have a mean for the general population of 50 and a standard deviation of 10. In the present study the means and standard deviations are presented in Table 2.

TABLE 2.—*Means and Standard Deviations for Three Diagnostic Groups on the Minnesota Multiphasic Personality Inventory*

		?	Lie	F	Hs	D	Hy	Pd	Mf	Pa	Pt	Sc	Ma
Brain damage	Mean	50.00	56.75	54.16	62.66	72.83	62.41	57.41	54.58	55.33	58.25	56.00	49.66
	S.D.	0	6.39	5.74	13.00	13.04	14.18	9.53	10.04	9.81	10.77	12.79	9.90
Multiple sclerosis	Mean	50.00	54.36	52.27	66.09	69.46	67.09	56.36	57.64	50.00	53.73	55.91	56.00
	S.D.	0	5.23	2.99	15.20	12.64	13.65	5.48	8.09	4.61	8.10	9.39	8.86
No brain damage	Mean	50.00	54.00	56.77	63.38	71.92	67.00	61.54	52.38	57.61	57.46	58.38	57.46
	S.D.	0	6.24	6.04	12.68	15.12	8.86	14.74	9.43	8.93	10.54	10.19	10.27

Table 2 indicates clearly that each group tends to be high on the scales composing the "neurotic triad," Hypochondriasis, Depression, and Hysteria. These results are even more apparent in a graphic representation of the mean values (Fig. 1).

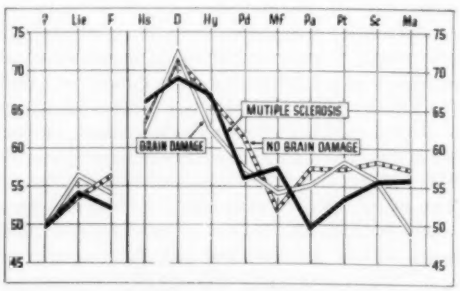

Fig. 1.—Graphic presentation of means for three diagnostic groups on the Minnesota Multiphasic Personality Inventory.

The three groups fall roughly within the normal range on the validity scales, ?, Lie, and F. None of these averages deviates substantially from the general population mean of 50, suggesting that the tests were carefully done and the results are trustworthy. The general similarity of the three profiles is striking, showing the highest scores on the Hypochondriasis, Depression, and Hysteria scales, but being roughly within the normal range on the remaining scales.

Statistical tests of the intergroup mean differences indicate that the patients with multiple sclerosis and those with organic brain damage do not differ significantly on any scale. Comparisons of the group with multiple sclerosis and the group without brain damage indicate that the latter group had a significantly higher mean on the F scale ($p<0.05$) and also on the Paranoia scale ($p<0.01$). The group without brain damage differed significantly from the brain-damaged group on only one scale, Mania ($p=0.05$). These results indicate that our patients without brain damage were probably a little more disturbed emotionally than were those with multiple sclerosis or with brain damage. These results bear out the adequacy of our deliberate attempt to compose, as a control group, patients without brain damage who not only were approximately equivalent in color, sex, age, education, and I. Q., but also had fairly severe affective and emotional disturbances.

Because our small groups may not be adequately representative samples of their populations, we do not wish to emphasize the statistically significant intergroup differences or to speculate with regard to their general application. It would seem more appropriate to note the general similarity of the profiles (Fig. 1) for the three groups and the general shape of the curves. The indication that the average profile for patients with multiple sclerosis emphasizes the "neurotic triad" of Hypochondriasis, Depression, and Hysteria has been pointed out by Baldwin [12] and Canter.[38] Our finding that the Minnesota Multiphasic Personality Inventory shows no substantial differences in the three groups has no necessary bearing upon the hypothesis that the etiology of multiple sclerosis may be emotional. Rather, the findings indicate that the measured end-result using this test is substantially the same in a neurotically ill group as in patients with organic cerebral damage. However, the fact that the group with brain damage shows no statistically significant differences from the group with multiple sclerosis, in spite of the fact that the average profiles in all three groups are quite typical of neurotic disturbances, might possibly be construed as an argument against the emotional etiology of multiple sclerosis. The presence of either brain damage alone or neurosis alone would seem to be a sufficient requisite for the average profile obtained, and therefore either or both of these factors may have contributed to the results for our patients with multiple sclerosis.

Tests of Biological Intelligence.—Halstead's [19] measures of biological intelligence indicate severe impairment in the brain-damaged group and in the multiple-sclerosis group, whereas the one without brain damage is generally in the normal range. Means and standard deviations on the Halstead Impairment Index and 10 "discriminating" tests, as well as 2 of the "non-discriminating" tests, are given in Table 3.

Although Table 3 gives details regarding central tendency and variability on the measures, a visual presentation of mean values makes the similarities and differences between groups apparent (Fig. 2).

Before we comment on the intergroup comparisons in Figure 2, the design of the chart should be explained. This profile chart was constructed in Halstead's laboratory on the basis of a large group composed of individually tested brain-damaged and control subjects (N=451). The heavy horizontal line represents the criterion level for each test which Halstead found to differentiate best his control and frontal-brain-damaged subjects. A test performance above the criterion line indicates a performance similar to those characteristic of Halstead's subjects with

TABLE 3.—*Means and Standard Deviations for Three Diagnostic Groups on Measures of Biological Intelligence*

		Halstead Impairment Index	Category	CFF	CFF-Dev.	Tactual Performance Test: Time	Tactual Performance Test: Memory	Tactual Performance Test: Localization
Brain damage	Mean	0.692	52.07	23.43	0.792	25.65	5.60	1.80
	S.D.	0.120	20.93	3.52	0.458	10.09	1.28	1.54
Multiple sclerosis	Mean	0.692	52.61	21.22	0.817	27.63	6.11	2.56
	S.D.	0.209	27.78	4.43	0.359	12.05	2.51	1.77
No brain damage	Mean	0.415	43.08	23.75	0.792	14.70	7.69	5.08
	S.D.	0.129	15.34	3.83	0.508	5.55	1.54	2.73

		Seashore Rhythm	Speech Perception	Finger Oscillation	Time Sense-Memory	Time Sense-Visual	Schem. Faces
Brain damage	Mean	9.77	13.61	46.69	520.64	126.37	5.92
	S.D.	0.58	5.98	4.80	495.46	145.45	3.85
Multiple sclerosis	Mean	8.15	13.17	36.84	293.78	125.25	5.46
	S.D.	2.71	8.26	9.92	229.46	146.14	3.75
No brain damage	Mean	5.62	6.08	49.46	333.90	55.31	3.38
	S.D.	4.11	4.14	5.81	209.21	29.94	3.65

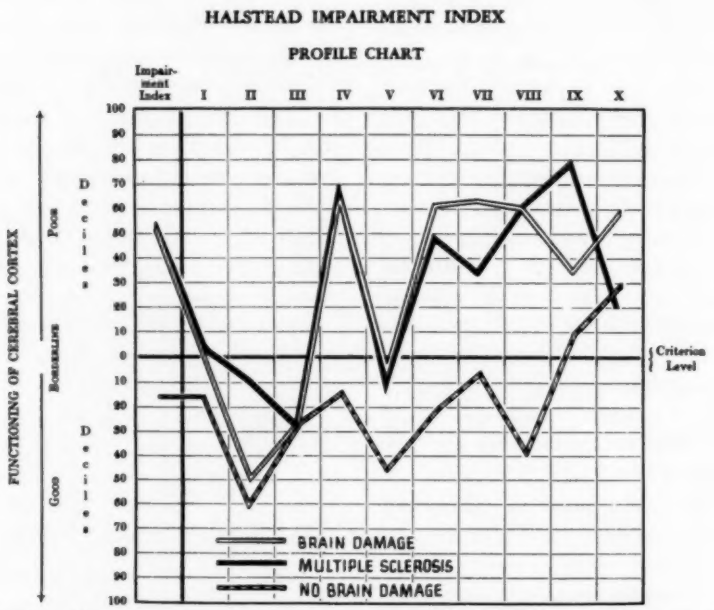

Fig. 2.—Graphic presentation of results obtained with three diagnostic groups on Halstead's tests of biological intelligence.

I, Category Test; *II*, Critical Fusion Frequency; *III*, Critical Fusion Frequency Deviation; *IV*, Tactual Performance Test (Time); *V*, Tactual Performance Test (Memory); *VI*, Tactual Performance Test (Localization); *VII*, Seashore Rhythm Test; *VIII*, Speech-Sounds Perception Test; *IX*, Finger Oscillation; *X*, Time Sense Test (Memory).

frontal brain damage, and a score below is in the control range. Deciles above and below the criterion level are indicated along the vertical axis. In Figure 2, the percentile rank of 55 on the Impairment Index, above the criterion line, for both the brain-damaged group and the multiple-sclerosis group indicates that their mean scores were at a level which is poorer than 55% of Halstead's patients who scored in the brain-damaged range on this variable. The group without brain damage had a mean Impairment Index

which was lower than only 15% of Halstead's subjects who scored in the normal range. This indication is in accordance with our deliberate effort to compose a group without brain damage but who were neurotically disturbed or had chronic illnesses.

The 10 tests which Halstead found to differentiate significantly between frontal-brain-damaged and control subjects are numbered along the horizontal axis of Figure 2. The Impairment Index is a composite score based upon these 10 tests, and is determined for an individual subject merely by counting the number of tests which fall above the criterion level. An Impairment Index of 0.7, then, indicates that a particular subject's scores on 7 of the 10 tests were in the range characteristic of frontal brain damage.

The general trend of the results shown in Figure 2 indicates that the mean values for the brain-damaged and the multiple-sclerosis groups tended to be quite similar, and that both generally fell in the range previously found to be characteristic of impaired biological intelligence. The results for the group without brain damage were generally in the "normal" range, but fell within the range typical of brain damage on two tests.

Before identifying and describing individual tests, it may be advantageous to present the statistical comparisons of the intergroup differences, which provide a basis for estimating the probability that the differences are other than sampling errors. Table 4 presents *t* ratios comparing each combination of groups.

Comparisons of the brain-damaged group and the multiple-sclerosis group yields only one *t* ratio which reaches statistical significance. The brain-damaged patients had a mean value on the Finger Oscillation Test which was higher than the mean for the patients with multiple sclerosis, beyond the 0.05 level of significance. In this test the score is obtained by averaging five trials of the tapping speed of the index finger of the preferred hand over a 10-second interval. While the patients with multiple sclerosis were poorer than the brain-damaged group on this performance, it is interesting to note that no signifiant differences were present upon tests that require more complex visuomotor coordination. The nature of these tests will be described in citing the significant differences in the remaining intergroup comparisons.

Comparison of the patients without brain damage and those with multiple sclerosis indicates that on 6 of the 10 "discriminating" tests the differences are significant beyond the 0.05 level. In addition, the Impairment Index differentiates these groups at a level of confidence beyond 0.0002. In each instance, the patients with multiple sclerosis obtained the poorer mean score. The tests which differentiated these groups are Critical Flicker Frequency ($p<0.05$); three components of the Tactual Performance Test, i. e., Time component ($p<0.0001$), Memory component ($p<0.05$) and Localization component ($p<0.01$); Speech-Sounds Perception Test ($p<0.05$, and Finger Oscillation

TABLE 4.—*Comparisons of Mean Differences in Three Diagnostic Groups on Measures of Biological Intelligence by Means of t Ratios*

	Halstead Impairment Index	Category	CFF	CFF-Dev.	Tactual Performance Test: Time	Tactual Performance Test: Memory	Tactual Performance Test: Localization
Brain damage-multiple sclerosis	0.00	—0.08	1.43	—0.13	—0.62	—0.68	—1.25
No brain damage-multiple sclerosis	—5.77	—1.56	2.58	—0.10	—6.56	2.61	3.61
Brain damage-no brain damage	6.35	1.47	—0.21	0	4.29	—3.28	—3.73

	Seashore Rhythm	Speech Perception	Finger Oscillation	Time Sense-Memory	Time Sense-Visual	Schem. Faces
Brain damage-multiple sclerosis	1.84	0.20	2.37	1.22	0.02	0.33
No brain damage-multiple sclerosis	—1.94	—2.63	3.59	0.41	—1.65	—2.10
Brain damage-no brain damage	3.49	3.51	—1.70	1.18	1.67	1.94

($p<0.01$). In order to clarify the abilities on which our patients with multiple sclerosis were deficient, it is necessary to describe briefly the above tests and to indicate what is required of the subject.

Test *II* in Figure 2 is the low-level critical flicker-fusion measurement. The apparatus uses a modified Type 631-B General Radio Strobotac as an electronic source of variably intermittent light, housed in a soundproof container. It has provision for rapid calibration of intensity and frequency of the light source. On this measure the patients with multiple sclerosis had lower flicker-fusion frequencies than either of the other groups, the difference when compared with that for the group without brain damage being significant beyond the 0.05 level. Although a low fusion frequency has previously been reported for one patient with multiple sclerosis,[39] this is the first report of group results, to our knowledge. It is important to note that the depression of critical flicker frequency is not a perfectly consistent phenomenon in multiple sclerosis. Although individual patients fused at points covering the entire range of our recorded frequencies, the tendency of the group was to fuse at low frequencies. Simonson and Brozek [40] have recently reviewed the evidence concerning the comparative roles of central and peripheral visual components in flicker fusion. They conclude that while flicker fusion is a complex phenomenon, the available evidence is overwhelmingly in favor of the functional significance of central rather than peripheral components. It would appear, therefore, that cerebral cortical damage or dysfunction was more influential in determining these results with our multiple sclerosis patients than possible peripheral visual involvement.

The Tactual Performance Test of Halstead's battery (Tests *IV*, *V*, and *VI* of Figure 2) makes use of a modification of the Seguin-Goddard form board. The subject is blindfolded and is not permitted to see the form board or blocks at any time. The subject fits the blocks into their proper spaces with his preferred hand, then repeats the procedure with his other hand, and finally performs the task a third time using both hands. After the board and blocks have been put out of sight, the blindfold is removed, and the subject is required to draw a diagram of the board representing the blocks in their proper places. The subject is scored for the total time needed to place the blocks, for the number of blocks correctly reproduced, and for the number correctly localized in his drawing. Each of these measures significantly differentiates the group with multiple sclerosis from that without brain damage.

Although the patients with multiple sclerosis needed nearly twice as much time as did those without brain damage to complete placing of the blocks, and consequently were exposed to the shapes of the blocks and their position on the board for a longer period, they were able to remember and localize fewer of the shapes in their drawings. None of the patients gave any clinical evidence of dystereognosis, nor was the slowness in placing the blocks the result of significant ataxia.

One might inquire whether the first component of this test (time required for placing the blocks) was unduly influenced by impairment of motor function in our patients with multiple sclerosis, or whether their poor performance might be an effect of impairment of the necessary intellectual functions. Although the patients with multiple sclerosis were significantly poorer than the brain-damaged group in speed of tapping—a motor task requiring little organizing and differentiating ability—there was no significant difference on the various scores of the Tactual Performance Test. The possibility still exists, of course, in the face of this evidence, that the poor performance of the brain-damaged group may be ascribed to impaired intelligence, while that of the multiple-sclerosis group was an effect of impaired motor function. While we do not have sufficient evidence to answer the question incontrovertibly, it is interesting to note that no significant differences in any of the three intergroup comparisons appeared in the Time-Sense Visual Test (Tables 2 and 3).

This test requires the subject to depress a key which permits a sweep-hand to rotate on the face of a clock. The subject's task is to permit the hand to rotate 10 times and then to stop it as close to the starting position as possible. The recorded score is the absolute amount of error in 40 trials, recorded in one-hundredths of a second. Although this test requires concentrated attention over forty 10-second intervals, together with fairly precise visuomotor coordination, the means for the three groups were not significantly different. This test is one of Halstead's "non-discriminating" tests, which he has included in the battery to indicate comparability of control and experimental groups in respect to visuomotor coordination, as well as in the ability to sustain concentrated attention. Our evidence suggests, then, that the impaired performance of the patients with multiple sclerosis on the Tactual Performance Test was more likely the result of a loss in the necessary intellectual functions than in motor ability.

The patients with multiple sclerosis also performed more poorly than did the group without brain damage on the Speech-Sounds Perception Test (Test *VIII*, Fig. 2). This test consists of 60 spoken speech sounds which are nonsense syllable variants of the ee digraph, presented in multiple-choice form. The test is played from a tape record with the intensity of sound adjusted to suit the subject's preference. His task is to select the spoken syllable from the alternatives printed on his test form. The patients with multiple sclerosis showed impairment in this task, which requires perception and discrimination of auditory stimuli.

Finally, the patients with multiple sclerosis obtained a significantly lower mean on the Finger Oscillation Test (Test *IX*, Fig. 2) than did those without brain damage. This test has been described above.

Comparison of the brain-damaged patients and those without brain damage indicates that the significant mean differences are roughly the same as those obtained in the comparison of the multiple sclerosis patients and those without brain damage. In this study the critical flicker frequency and speed of finger oscillation are not significantly different in the patients with and those without brain damage. The Rhythm subtest of the Seashore Test for Musical Talent indicates reliable impairment in the brain-damaged group on this variable. With the above exceptions, the same tests differentiate the means of the patients without brain damage from the other two groups. It would appear from our results that the measures of biological intelligence show impairment which is comparable in both kind and degree in the brain-damaged patients and in patients with multiple sclerosis.

Another "non-discriminating" test, the Schematic Faces Test, failed to show any significant differences between the groups. This test consists of nine schematic faces selected from the series developed by Brunswik and Reiter [41] which are presented in different groupings on two separate cards. The subject is given a list of characteristics representing polar extremes, such as "gay" and "sad," "beautiful" and "ugly," and asked to select the face which best represents each characteristic. Halstead [42] has found from studying large groups of brain-damaged, mentally ill, and control subjects that each group shows a common, remarkable consistency (far above chance expectancy) in selecting certain schematic faces for pleasant characteristics and certain other faces for unpleasant characteristics. Halstead has cited this result as an illustration of categorizing without regard for rational principles, which may remain stable in the face of brain damage or mental illness. It would also seem to represent an ability to conform to a common stereotype with regard to the relative positions of facial features, and perhaps a consistent, though possibly largely irrational, sensitivity to the emotional nuances in interpersonal relationships which may be conveyed through facial expressions. Although our groups with brain damage and multiple sclerosis both had more reversals on the average than the group without brain damage, the intergroup mean differences were not sufficiently large with

TABLE 5.—*Means and Standard Deviations for Three Diagnostic Groups on Rorschach Test Variables*

		R	W	D	Dd	M	SumC	Z	F+	F—	Tot F
Multiple sclerosis	Mean	14.69	7.15	6.92	0.62	1.23	2.58	26.38	6.15	2.46	8.69
	S. D.	4.36	1.61	4.03	0.74	1.53	1.43	7.95	3.46	1.34	3.69
Brain damage	Mean	13.00	6.62	6.15	0.23	0.77	1.81	23.69	6.15	1.85	8.00
	S. D.	3.49	1.15	3.06	0.55	0.80	1.43	6.43	3.16	1.51	3.26
No brain damage	Mean	28.85	7.85	18.92	2.08	2.85	4.73	36.77	12.00	2.85	15.69
	S. D.	19.92	4.99	16.21	3.27	2.98	3.06	23.72	7.77	3.82	12.14

		CF	FC	TotC	YF	FY	TotY	S	P	T/R	Z T/R
Multiple sclerosis	Mean	1.69	1.08	3.00	0.15	1.00	1.15	0.54	4.31	52.56	0.64
	S. D.	0.99	0.83	1.02	0.53	1.11	1.35	0.84	1.77	29.25	0.34
Brain damage	Mean	1.00	1.38	2.46	0.23	1.15	1.38	0.69	4.46	55.32	0.46
	S. D.	1.04	1.44	1.82	0.58	0.86	1.15	0.72	1.69	13.51	0.18
No brain damage	Mean	3.31	2.38	5.77	1.31	2.38	3.77	2.62	5.92	56.25	0.84
	S. D.	2.09	3.03	4.90	1.49	2.92	3.85	2.73	3.75	25.75	0.53

relation to variability of the scores to reach statistical significance.

Rorschach Test.—The results obtained with the Rorschach Test are similar to those found with Halstead's tests. Table 5 presents the means and standard deviations for the three groups on various Rorschach variables.

The mean values in Table 5 fall fairly consistently in the following order from highest to lowest: no brain damage, multiple sclerosis, and brain damage. This trend is easier to observe in a graphic representation of the mean values. Figure 3 portrays the mean values for each group, with each variable indicated on an equivalent scale.

The equivalent scale for the Rorschach variables, which is presented along the ordinate of Figure 3, was constructed by combining the three groups and converting the raw scores for each variable into T-scores. The ordinate is, therefore, a T-score scale with a mean of 50 and a standard deviation of 10. The raw score means for each group were plotted on the graph in accordance with their equivalent T-scores. It is possible with this graph, then, to estimate the degree of variance of each group mean from the mean for the combined groups, which is 50 for each variable. Perhaps the major advantage of this type of graph for our purpose is that it permits an evaluation of the general trend in comparing the groups.

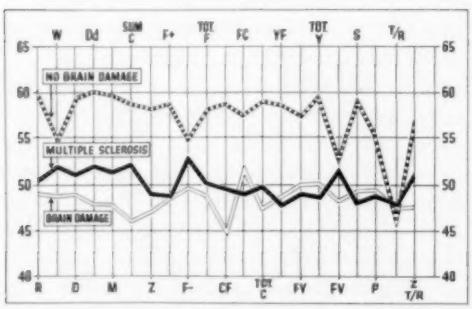

Fig. 3.—Graphic presentation of results obtained with three diagnostic groups on the Rorschach test.

It will be noted that the mean scores for the group without brain damage regularly exceed those for the other groups. The considerable extent of the differences becomes obvious upon recalling that 10 points on either side of the mean for the three groups (a T-score of 50) represents one standard deviation. The group with multiple sclerosis generally has higher means than the brain-damaged group, but the differences are neither very consistent in direction nor striking in magnitude.

The nearly complete lack of overlap in Figure 3 of the groups with brain damage and multiple sclerosis as compared with the group without brain damage argues strongly that there is a real difference as measured by the Rorschach Test. However, the fact that some of the Rorschach variables are interdependent measures introduces some difficulty in interpretation of the graph. For example, the number of whole responses (W) obviously is limited by the total number of responses (R), and since R is higher

in one group than another, one would expect that W also might be higher. While dependency of this type undoubtedly makes some contribution to the trend shown in the graph, a number of the variables are independent measures. The lack of reversals among these independent measures, except for time per response (T/R), suggests that the graph does portray a trend which is more than statistical artifact.

Table 6 presents the *t* ratios which indicate the probability that the mean differences considered individually may be attributed to chance.

For 12 degrees of freedom, a *t* ratio of 3.06 is needed to reach the 0.01 confidence level, 2.68 for the 0.02 level, and 2.18 for the 0.05 level. None of the ratios comparing the group with multiple sclerosis and that with brain damage reach the 0.05 confidence level. Seven of the ratios comparing the group without brain damage and the multiple sclerosis group exceed the 0.05 level. The variables on which these significant differences occur are (1) the total number of responses, (2) the number of responses using major details, (3) the number of "human movement" responses, (4) the number of responses using both color and form, but in which color was the major determinant, (5) the number of responses using surface shading and form, but in which surface shading was the major determinant, (6) the total number of responses using surface shading, and (7) the number of responses involving the white spaces on the ink blots. Comparisons of the groups with and without brain damage indicate significant differences on all of these same variables except for the total number of responses using surface shading. In addition, however, these latter groups differ significantly with respect to the total use of color in forming associations (Sum C) and the speed with which they could impose organization upon the diverse aspects of the ink blots ($\frac{Z}{T/R}$).

A detailed interpretation of these quantitative differences, in consideration of the small groups used in this study, might well be presumptuous. It would seem legitimate, however, to conclude that the group with multiple sclerosis appears to be much more similar to the brain-damaged group than the group without brain damage. The Rorschach results suggest an impairment of the ability to associate spontaneously to the relatively unstructured stimulus material of the ink blots in both our multiple-sclerosis and our brain-damaged groups.

TABLE 6.—*Comparison of Mean Differences in Three Diagnostic Groups on Rorschach Test Variables by Means of* t *Ratios*

	R	W	D	Dd	M	SumC	Z	F+	F−	Tot F
Multiple sclerosis-brain damage	1.06	1.10	0.49	1.19	0.96	1.28	0.97	0	1.11	0.41
No brain damage-multiple sclerosis	2.30	0.46	2.40	1.42	2.35	2.05	1.67	2.10	0.37	1.82
No brain damage-brain damage	2.60	0.82	2.62	1.93	2.19	2.37	1.96	2.16	1.05	2.08

	CF	FC	TotC	YF	FY	TotY	S	P	T/R	$\frac{Z}{T/R}$
Multiple sclerosis-brain damage	1.50	−0.56	0.68	−0.33	−0.31	−0.38	−0.62	−0.28	−0.28	1.51
No brain damage-multiple sclerosis	2.25	1.68	2.08	2.47	1.62	2.22	2.34	1.23	0.33	1.24
No brain damage-brain damage	3.21	0.93	2.03	2.30	1.27	1.86	2.46	1.07	0.11	2.43

As another approach to the possible quantitative differentiation of the three groups, the Rorschach records were studied with reference to the frequency of occurrence of various "signs" of impaired psychological functions associated with organic brain damage. Four of the 10 signs proposed by Piotrowski [31] were used, together with 8 of the 9 that were proposed by Aita, Reitan, and Ruth.[33] Although the psychological meaning of these signs has not been completely established or clearly differentiated, their relevance to brain damage * and to intellectual losses associated with brain

* References 31 and 33.

damage has been indicated, in the latter instance by their significant relationship † to Halstead's [19] measures of biological intelligence.

Figure 4 presents a graphic comparison of the relative frequencies with which the signs occurred in each group. Each sign is indicated on the horizontal axis. "Most," "Middle," and "Least" along the vertical axis indicate the relative frequency of the signs in the three groups. When the same frequency in two groups occurred for a particular sign, both groups are indicated at an average of the two positions not occupied by the third group.

It is apparent from Figure 4 that the definite trend noted both with the measures of biological intelligence and with the previous Rorschach data is again present. The group without brain damage tends consistently to have the smallest number of signs, and the groups with multiple sclerosis and brain damage are rather closely equivalent. A statistical evaluation of the frequency differences among the groups was made using the χ^2 test, computed with Yates' correction for continuity because of the small groups. Although few of the individual signs differentiated the group without brain damage from the other two groups at statistically significant levels, a greater total number of signs occurred in both the brain-damaged and the multiple-sclerosis groups at a high level of confidence ($p<0.001$). The total number of signs was almost equal in the groups with multiple sclerosis and brain damage. These results suggest that if larger groups were used and Yates' correction was unnecessary, more of the differences on individual signs would have been significant.

An over-all view of the quantitative results obtained with the Rorschach Test indicates that the groups with brain damage and multiple sclerosis showed only small differences, which without exception failed to reach statistically significant levels. The group with multiple sclerosis differed in similar ways, and to nearly the same degree, from the group without brain damage as did the brain-damaged patients.

†Reitan, R. M.: Relationship to Certain Rorschach Variables to the Abstraction and Power Factors of Biological Intelligence, unpublished doctorate's thesis, University of Chicago, 1950.

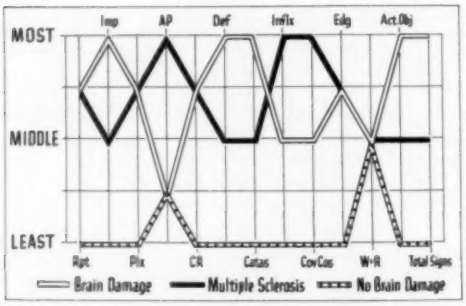

Fig. 4.—Comparative frequency of occurrence of Rorschach Test "signs" of brain damage in three diagnostic groups. *Imp*, impotence, or the recognition of the inadequacy of a response, with inability either to improve or to withdraw it; *Plx*, perplexity, or the subject's distrust of his own ability, with seeking for reassurance from the examiner; *AP*, automatic phrases, or the use of a stereotyped phrase in an indiscriminate manner in more than half the cards; *CR*, concrete response, or failure to give a single response characterizing a quality or attribute of the object mentioned; *Def*, unclear definition, or inability to point out clearly the specific details of responses; *Catas*, catastrophic reaction, or an overt emotional display expressing frustration arising from the test situation; *Inflx*, inflexibility, or failure in the entire record to use any part of an ink blot for more than one association; *CovCds*, covering parts of cards while attempting to formulate associations; *Edg*, edging, or holding the card at unusual angles, peering at it from a side view, etc.; *W+R*, withdrawal and reattack, or voluntary withdrawal of attention from the ink blot only to return with new vigor; *ActObj*, consideration of the ink blots as representative of actual objects.

COMMENT

Our results indicate that intellectual losses occur in a high proportion of patients with multiple sclerosis, including some who show no obvious mental deterioration according to usual clinical standards. In addition, our findings corroborate the presence of neurotic-like affective disturbances characterized primarily by anxiety, depression, hysteria, and persistent concern regarding physical functions. Although the patients with multiple sclerosis were carefully matched with brain-damaged and non-brain-damaged patients on criteria which might possibly influence the results in ways irrelevant to the questions being asked in this

study, the mean scores on the tests which previously have been found sensitive to intellectual impairment from brain damage consistently differentiated the group with multiple sclerosis and that with brain damage from the group without brain damage. We have adopted a cautious attitude toward overly detailed interpretation of the results in this study according to the degree to which we estimate our groups to be representative of populations of the diagnostic categories compared. Although there was unequivocal evidence substantiating the diagnosis of each patient included, the size of the groups is sufficiently small to cause serious misgivings as to whether our patients with multiple sclerosis, for example, are representative of the total population from which they were drawn. Although the statistical evidence reveals many differences which could hardly have occurred on a chance basis, we have no assurance that differences on other tests which approached but did not reach statistically significant levels might not receive comparable emphasis in a study of larger groups. A statistical finding which does not disprove the null hypothesis cannot be assumed to prove that the populations are not significantly different. For this reason we have emphasized only the differences in trend in our comparable samples, rather than attempted to propose a syndrome of mental changes characteristic of multiple sclerosis.

Since this study provides an independent evaluation of the validity of Halstead's tests of biological intelligence, this aspect of the results is worthy of additional brief comment. The results give general substantiation of the sensitivity of this battery to brain damage. Of the tests used, this battery revealed differences between groups with and without brain damage which were by far the largest with relation to the variability of differences. The Halstead Impairment Index, for example, yielded a mean difference between the groups with and without brain damage that was significant beyond the 0.0002 level. The validity of Halstead's battery as judged from this study agrees almost perfectly with the findings of a larger study,[43] and confirms the sensitivity of these tests to brain damage.

Our results suggest that intellectual impairment in multiple sclerosis may be almost as important a component of the complete medical picture as in proved brain damage. Because of this indication, together with the paucity of experimental results on this problem reported in the literature, the value of encouraging further study should be emphasized. Should the finding of such impairment in multiple sclerosis be substantiated in studies of larger and more representative groups, it would be of value to recognize these aspects among the symptoms of the disease.

SUMMARY

Widely divergent estimates have been reported regarding the incidence and extent of intellectual impairment in persons having multiple sclerosis. Some are based upon clinical impressions only; others are conclusions reached by the use of single psychological tests or batteries which have proved of inconsistent validity in organic brain damage. In the present study, an extensive series of tests was used; the results were analyzed statistically, and the findings were correlated.

Three groups of 13 patients each were used. One was composed of an unselected series of patients with multiple sclerosis; a control group consisted of patients with proved brain damage, and another control series was made up of patients having no history or evidence of damage to the brain. Each patient was matched with a corresponding one in the other groups on the basis of color, sex, age, number of years of formal education, and Wechsler-Bellevue full-scale Intelligence Quotient.

The tests administered to each patient were the Minnesota Multiphasic Personality Inventory, Halstead's tests for measurement of biological intelligence, and the Rorschach Test. Halstead has presented evidence indicating that his battery measures aspects of intelligence which are particularly suscepti-

ble of impairment with brain damage, but are not closely correlated with I. Q. measures.

The profiles of all three groups were similar on the Minnesota Multiphasic Personality Inventory and were quite typical of neurotic disturbances. On the other hand, Halstead's battery indicated severe and parallel intellectual impairment in a high percentage of patients in both the multiple sclerosis group and the group with brain damage. The Rorschach Test indicated similar impairment, but of less striking magnitude. The findings in the group without damage to the brain, in contrast, were generally within the normal range.

Although the samples are small, the results indicate a statistically valid trend which warrants similar investigations of larger series.

CONCLUSIONS

This study suggests that, in addition to affective disturbances, impairment of intellectual functions occurs in a high proportion of persons having multiple sclerosis. Cognizance of these facets of the disease should be valuable to the physician in assisting the patient to adjust to his problems with maximal efficiency within the framework of his limitations.

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Papilledema in the Guillain-Barré Syndrome

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The thinking about the Guillain-Barré syndrome has undergone considerable change since its first description, in 1916, as a syndrome of polyradiculoneuritis with albuminocytological dissociation ending in recovery. It became apparent that the original description should be broadened, and in 1940 De Jong [1] recognized cases with a short duration and a favorable prognosis, cases with a prolonged or chronic course, and, finally, those terminating fatally. Later the bulbar, the cerebellar, and the cerebral forms were described and the involvement of the cranial nerves emphasized. These various forms of the syndrome have been fully reviewed recently by Guillain,[2] who described the syndrome originally.

Papilledema is very rarely associated with the Guillain-Barré syndrome, and the literature on this subject was reviewed in 1951 by Drew and Magee,[3] who collected nine cases and added another. In some of the cases reviewed the cerebrospinal fluid (C. S. F.) pressure was increased, while in others it was normal. The range of papilledema reported varied from "slight" to 3 D., and the C. S. F. protein content, from "increased" to 2080 mg. per 100 cc.

Since then, an additional four cases of the Guillain-Barré syndrome with papilledema have been found in the literature. Krohn [4] relates the case of a patient who developed papilledema with retinal hemorrhages two months after the onset of the disease and who recovered without any special treatment a few weeks later. When the papilledema was decreasing, the C. S. F. protein was still 624 mg. per 100 cc. The electroencephalogram was normal. In another case, reported briefly by Dereux,[5] the pneumoencephalogram was normal. Surgical decompression was considered necessary because of the increased intracranial pressure. Ford [6] reports the history of a 9-year-old child who developed polyneuritis after a mild upper respiratory tract infection. The C. S. F. pressure was 280 mm. with elevated protein but without excess of cells. During convalescence cerebellar ataxia and papilledema appeared, lasting about one month. Denny-Brown's [7] case is of special interest because of the autopsy findings. The papilledema appeared in the seventh week of the disease and was associated with a C. S. F. pressure of 390 mm. The protein content was 286 mg. per 100 cc., and the spinal fluid clotted spontaneously in the test tube. After repeated lumbar punctures the papilledema subsided, but the patient died of intercurrent pneumonia. At autopsy the Pacchionian bodies were uniformly plugged with amorphous material, which was beginning to show recanalization. No adhesions or other cause of hydrocephalus was found.

For more than a year we have had the opportunity of observing a patient suffering from the Guillain-Barré syndrome with papilledema. Though the only cerebral manifestation in our case, as in most of the similar cases reported, was the papilledema, its presence raises interesting problems as to the pathogenesis of the increased intracranial pressure. Because of the rarity of this finding, the prolonged period of observation, and

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the development of the syndrome during Rh immunization in pregnancy, our case is reported.

REPORT OF A CASE

L. S., a woman aged 23, was admitted to the Department of Neurology because of weakness in her extremities and bilateral papilledema. She had been married for three and a half years and had had two pregnancies, both of them ending in death of the infant shortly after delivery, because of erythroblastosis fœtalis. Her blood group was A M Rh-negative, whereas her husband's was Rh-positive (homozygote). During her first pregnancy, in 1951, she suffered from severe vomiting. Her second pregnancy began in July, 1952, and this time, also, the patient vomited; but these attacks stopped at the end of the fifth month of pregnancy.

At the beginning of her second pregnancy the patient began suffering from pain in her legs, associated with peculiar sensations, especially in the calves and soles. In the fourth month she complained of frontal headaches and waves of heat over her face. The abnormal feeling in her legs developed into a burning sensation, appeared in her hands as well, and increased to such an extent that she had to cool her hands in ice water. A month later, that is, in her fifth month of pregnancy, she experienced weakness in her legs. As pregnancy progressed her condition deteriorated, so that by the end of gestation she could hardly walk. In the eighth month she delivered a child, who died 24 hours later of erythroblastosis fœtalis.

Following delivery, her condition deteriorated even more and her walking was limited to a few steps with support. At that time definite weakness appeared in her hands as well. Three weeks after delivery, in March, 1953, she was admitted to another hospital. On admission, she was unable to stand or walk; there were weakness, atrophy, and hypesthesia in the distal parts of her hands and feet, reduced deep sensitivity in her legs, and loss of the knee and ankle reflexes. Bilateral papilledema was found. Lumbar puncture revealed 470 mg. of

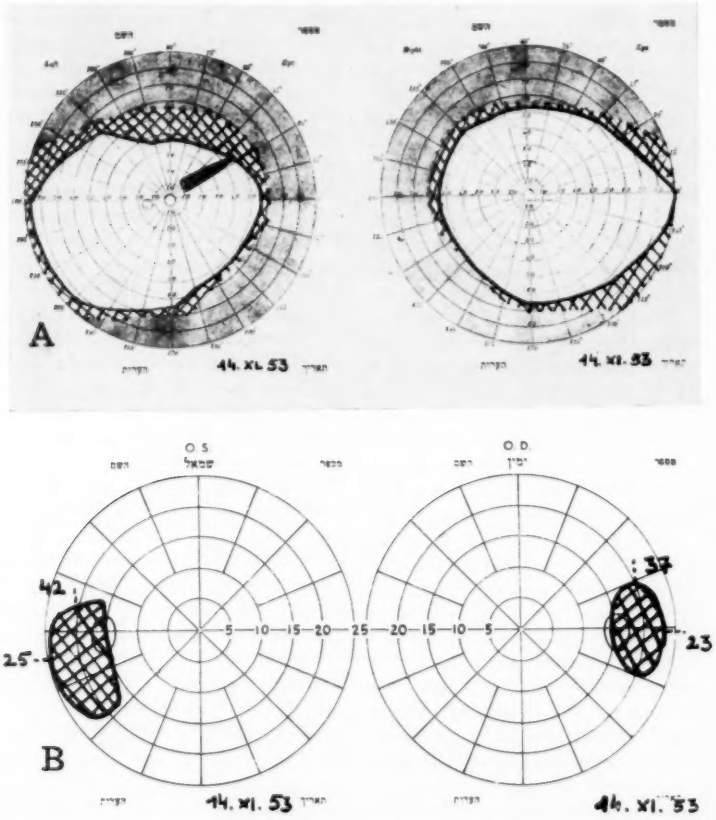

Fig. 1.—Upper, visual fields in November, 1953. Lower, Bjerrum screen test in November, 1953.

protein per 100 cc. and 2 white cells per cubic millimeter in the C. S. F., and a second examination of the fluid showed 540 mg. of protein per 100 cc. The C. S. F. pressure was not reported. Two months later she was transferred to another hospital, where the previous findings were confirmed, but some improvement in muscular power was noted. Clinical examination, as well as the various laboratory findings, were within normal limits. The Coombs test showed Rh antibodies in her blood, and on lumbar puncture 508 mg. of protein per 100 cc. and 2 white cells per cubic millimeter were found. Therapeutic trials with intravenous corticotropin for five days and with dimercaprol U. S. P. (BAL) were without effect. At that time there was some further improvement in muscular power and a considerable decrease of pain in her legs, but the paresthesiae persisted. After leaving the hospital she was able to walk short distances without support and to do simple housework. The pain disappeared completely, and she experienced only occasional slight paresthesiae.

She was admitted to the Department of Neurology of this hospital in November, 1953, for further investigation and for possible alleviation of the increased intracranial pressure. On admission she was in a good general condition and did not complain of headaches or of vomiting. She said that her vision was satisfactory, though she suffered from transitory blurring at times. On examination, we found considerable weakness of her hands and legs, with minimal movements in her feet. There was marked atrophy of the small muscles of her hands and of the calves. The reflexes were absent in her legs and markedly reduced in her arms. There were no changes in superficial sensitivity, but the appreciation of vibration was reduced in her legs and the appreciation of position was absent in the toes. Papilledema of 3 D. was found in the right eye and of 4 D. in the left eye, without venous engorgement or hemorrhages. The appearance of the blood vessels and the ratio of the caliber of the arteries to that of the veins were normal. Visual acuity was normal, but both blind spots were considerably enlarged, more in the left eye than in the right eye. The visual field of the right eye was normal, but the left showed a tongue-shaped scotoma in the superior nasal quadrant (Fig. 1). Lumbar puncture revealed a clear fluid under pressure of 305 mm., which contained no cells but 500 mg. of protein, mostly albumin, per 100 cc. The colloidal gold curve was normal. The glucose in the C. S. F. was 84 mg. per 100 cc., and the Wassermann reaction was negative. The electroencephalogram showed a slight generalized disturbance in brain activity. The chemical and serological examinations of the blood and the blood count, as well as the sedimentation rate, were normal. The x-ray of the skull showed no abnormality.

As our purpose was to alleviate the increased intracranial pressure, which might eventually produce secondary optic atrophy, lumbar puncture was repeated at intervals and the intracranial pressure was lowered by withdrawing between 10 to 15 cc. of C. S. F. at a time. During the same period control neurological and ophthalmological examinations were made. A course of intramuscular corticotropin was administered, but apparently without effect on the C. S. F. pressure or protein, though some of the lowest readings were obtained during this treatment. During her stay in hospital she was given physical therapy. She left the hospital in January, 1954, and was readmitted in March for further observation and treatment. At that time, in comparison with the previous examinations some improvement in her muscular power was noted, and deep sensitivity was found to be normal. The C. S. F. findings were essentially the same. Ophthalmological examination showed normal vision and the same visual fields, but the blind spots in both eyes had decreased slightly. During her third period of hospitalization in our department, in May, 1954, we found further improvement in power in her legs, but the C. S. F. pressure was still 340 mm. and the fluid contained 239 mg. of protein per 100 cc. without cells. In view of the failure of repeated withdrawals of C. S. F. to affect the pressure, and of the satisfactory ophthalmological findings, she was discharged from the hospital and was followed up in our outpatient clinic. She was readmitted to our department in July, 1954, for another lumbar puncture. The C. S. F. examination showed 120 mg. of protein per 100 cc., with a pressure of 280 mm. Ophthalmological examination showed a definite regression of the papilledema; vision was normal and the visual fields were the same, but the blind spots had further regressed since the previous examinations. The electroencephalogram was essentially the same. In July, as well as in December, 1954, a constant improvement was noted in muscular power, especially in the hands, but she still had difficulty in walking. The reflexes were absent in her legs but normal in her arms. In December her vision was normal and fundal examination showed no papilledema but some pallor in the inferotemporal part of the discs. The blood vessels, as on previous examinations, were normal in all respects. The visual fields showed a relative scotoma in the superior nasal quadrant of both eyes, more conspicuous in the left. The Bjerrum screen test showed enlarged blind spots. The left blind spot was connected with the relative central scotoma (Fig. 2). These visual field changes corresponded with the incipient optic atrophy observed in both discs. Results of titration of the patient's serum with her husband's red cells in January, 1955, showed a reading of 1 : 8 + in the indirect Coombs test and of 1 : 2 + with trypsinated cells. The C. S. F. pressure

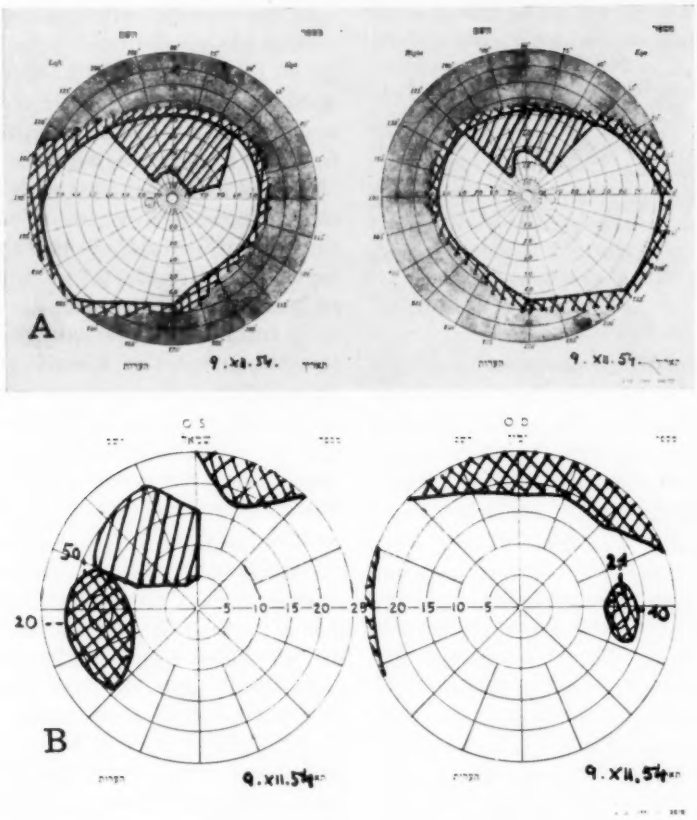

Fig. 2.—Upper, visual fields in December, 1954. Lower, Bjerrum screen test in December, 1954.

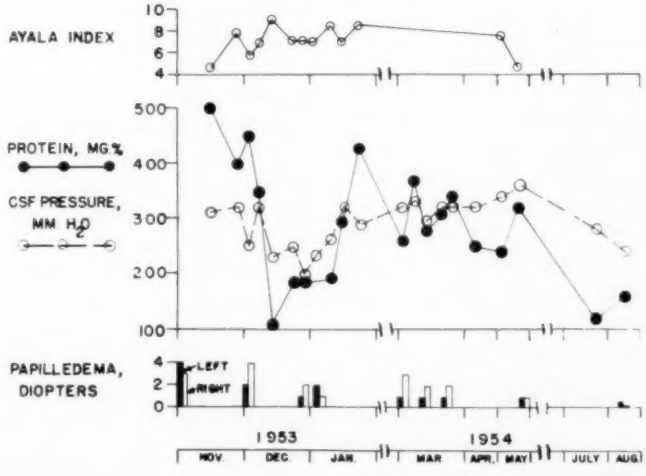

Fig. 3.—C. S. F. protein and pressure, degree of papilledema, and Ayala index during the observation period.

and protein content, as well as the changes in the height of the papilledema during the period of observation, are shown in Figure 3. The Ayala index, calculated by multiplying the quantity of C. S. F. removed by the final C. S. F. pressure, and dividing by the initial C. S. F. pressure, is also indicated. It will be noted from this Figure that in spite of repeated withdrawals of C. S. F. and the lowering of the pressure on each occasion to almost normal levels, subsequent examination showed the pressures to have returned to their previous values.

COMMENT

Any comment on the pathogenesis of papilledema in the Guillain-Barré syndrome must take into account the increased protein content of the C. S. F. There seems, however, to be some disagreement as to its origin. While some think that the protein molecules gain entry to the subarachnoid space from the congested nerve roots,[7] others have expressed the opinion that obliteration of the perineural spaces by the extremely swollen radicular trunks blocks the spinal fluid absorption along the perineural spaces. This leads to stagnation of fluid, which is associated with considerable increase in its protein content.[8] It can be assumed, however, that both these mechanisms operate in the production of the increased protein content of the C. S. F. in this syndrome.

One of the factors determining the C. S. F. absorption is the size of the stomata leading into veins and lymphatic channels, as these may be blocked by colloidal clots. Furthermore, all spinal fluids with a high protein content have a higher viscosity than normal spinal fluid and so have less tendency to be absorbed.[9] This fact has been emphasized recently in animal experiments, where it has been shown that the addition of autologous serum protein caused the rate of absorption from the subarachnoid space of Ringer's solution in the test animal to fall to approximately a fourth of the rate in the control.[10] Furthermore, it has been shown in recent experiments on C. S. F. circulation with isotopic tracers that C. S. F. protein is absorbed largely from the subarachnoid space, presumably from the arachnoid villi.[11]

In the Guillain-Barré syndrome both the possible plugging of these stomata by clotted C. S. F., as suggested in Denny-Brown's case, and the high protein content probably contribute to diminished absorption, and subsequently to the increased C. S. F. pressure, causing in rare cases external hydrocephalus and papilledema. The role of increased protein content in the C. S. F. as the cause of increased intracranial pressure has also been suggested by Gardner and his associates.[10] They advanced the opinion that papilledema reported in cases of acoustic neurinomata, poliomyelitis, ependymomas of the cauda equina, and the Guillain-Barré syndrome was due to mechanical clogging by the protein molecules of the semipermeable membrane that constitutes the brain-blood barrier.

There seems to be some similarity in the pathogenesis of the increased intracranial pressure in the Guillain-Barré syndrome and that in cases known as "pseudotumor cerebri" associated with thrombosis of the superior sagittal sinus. In these cases, recently reviewed by Wagener,[12] there is obstruction to absorption of C. S. F. by the Pacchionian bodies and the superior sagittal sinus, causing increased intracranial pressure and papilledema. There are a number of reported cases where the occlusion of the sinus, in association with the increased intracranial pressure and papilledema, has been demonstrated by venography. These findings suggest further that the papilledema in the Guillain-Barré syndrome may likewise be caused by the obstruction of C. S. F. absorption by the Pacchionian bodies.

The Ayala index determinations in our patient showed high values on a number of occasions. This finding suggests that the increased intracranial pressure is not due to cerebral edema, but is caused by an increased volume of C. S. F. The electroencephalogram has been reported as normal in two other cases,* and it was only slightly disturbed in our patient. This finding, as well as the absence of headaches and vomiting and the mental alertness of our patient, is further

* References 4 and 13.

evidence against the existence of a recognizable cerebral edema in this case.

The mechanism of the papilledema in the Guillain-Barré syndrome has been discussed by Drew and Magee,[3] and various possible causes have been mentioned. Some questions remain unanswered, however—for example, the appearance of fundal hemorrhages in association with the papilledema in most cases and the normal appearance of the blood vessels in others. It is very difficult, in fact, to explain the appearance of the retinal blood vessels in our patient, which were normal throughout the period of observation, in spite of the long-standing increased intracranial pressure and papilledema.

It is evident that our patient is suffering from the chronic form of the Guillain-Barré syndrome. Such a course results in permanent damage to the nervous system, although in rare cases complete recovery—even after three years—has been reported.[2]

The duration of papilledema in our patient seems to be the longest in similar cases published to date, as it has lasted one and a half years, approximately. The papilledema of 4 D., as observed on admission to our department, seems to be the highest value recorded in the Guillain-Barré syndrome with papilledema. In view of the increased C. S. F. pressure, as measured during the last lumbar puncture, and the visual field changes, the regression of the papilledema should be ascribed to developing optic atrophy.

The development of the disease during pregnancy, with maximum disability shortly after delivery, merits special consideration. A similar case has been reported by Ford and Walsh.[13] Their patient developed a progressive picture of polyradiculoneuritis during pregnancy, which was accompanied by severe vomiting. After delivery she was unable to walk, but showed some improvement later. Three months after delivery, bilateral papilledema was discovered, and the C. S. F. pressure was found to be 600 mm of water. The C. S. F. had 400 mg. of protein per 100 cc. and 6 cells per cubic millimeter. The ventriculogram was normal. Because the papilledema was associated with retinal hemorrhages, a subtemporal decompression was performed.

The pathogenesis of the Guillain-Barré syndrome is not entirely understood, but there is clinical evidence to suggest that the syndrome might be a late neuroallergic reaction, as the neurological complication in many cases follows bacterial and viral infections, as well as vaccinations and serum injections, after a latent period. The pathological picture of edema of the nerve fibers and the rapid response of the disease to corticotropin or cortisone in many acute cases lend further support to the allergic theory. The Rh status of the patient of Ford and Walsh was not determined, but in our case the disease seems to have progressed parallel with Rh immunization in pregnancy, and it attained its greatest severity when theoretically the immunization was at its maximum. One can only wonder as to the possible relation of the Rh immunization and the development of the Guillain-Barré syndrome in our patient.

SUMMARY

A short review of the recent literature on the occurrence of papilledema in the Guillain-Barré syndrome is given, and an additional case, which has been under observation for more than a year, is reported. The disease developed during pregnancy, and its progression seems to have been associated with Rh immunization. The papilledema has lasted about one and a half years, the longest period in any similar case reported to date. The retinal blood vessels were normal throughout the whole period of observation. The increased protein content of the C. S. F. as a causative factor in the production of papilledema in the Guillain-Barré syndrome has been emphasized. It has been suggested that the increased intracranial pressure is the result of diminished C. S. F. absorption.

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News and Comment

SOCIETY NEWS

American Psychosomatic Society.—At the annual business meeting of the American Psychosomatic Society, held on May 4, 1955, in Atlantic City, the following persons took office: Stanley Cobb, M.D., president, and I. Arthur Mirsky, M.D., president-elect.

Elected to Council positions were William J. Grace, M.D.; William A. Greene Jr., M.D.; Morton F. Reiser, M.D., and Philip F. D. Seitz, M.D.

The 30th annual meeting of the American Psychosomatic Society will be held on March 24 and 25, 1956, at the Sheraton Plaza, in Boston.

The Eye-Centering System

A Theoretical Consideration

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Just as there is a mechanism which pulls the eyes away from the center of gaze, so must there be a mechanism which brings the eyes back to the central position. The validity of a hypothetical mechanism of eye centering can be discerned in the following clinicopathologic and experimental studies of man and monkey.

In normal man and monkey all eye movements are bilateral, whereas motor acts in the rest of the body may be unilateral or bilateral. Discrete unilateral as well as bilateral movements can occur in the face, neck, trunk, and extremities, but it is quite unusual for man to move one eye at will. Both eyes move synchronously for any given performance. Not only do they move at will rapidly and with great precision in any desired direction, but they coordinate in such a way that the requirements of binocular vision are met without the occurrence of diplopia. Teleologically, this implies that in all ocular movements there must be a sensitive interaction so that corresponding areas of each retina are projected to the same point in space. It should be noted that this coordination is not invariable or structurally determined, for if the normal alignment of fixation is distorted by placing a weak prism in front of one eye, coordinated movements still occur without diplopia, showing that the relative adjustment between the two eyes may be maintained even though the alignment of one of them is altered. Moreover, when one is sleepy or if the neuromuscular coordination is blunted by barbiturates or alcohol, diplopia may result, demonstrating that the relation between the two eyes is less accurately maintained, possibly owing to interference with a mechanism which keeps them together. Here let us assume that it is the eye-centering mechanism which keeps the eyes together.

In no movement of the eyes does any single muscle act alone. This is a principle which applies for any motor performance in the body. Even in the discrete movement of one finger or in the blink of one eye there is more than one muscle in action. In all of their activities groups of ocular muscles contract together, while the antagonizing muscles relax in tone by reciprocal innervation; all of these effects are patterned in space and time. In this way finely graded movements are executed, not only by the interplay between the lines of force of the various contracting muscles, but also owing to the stabilizing and checking influence of the antagonists. It is assumed that this interaction between the protagonists and the antagonists tends to make the movement smooth and to prevent overaction. This effect is not a simple reflex mechanism. Not only are the muscles of the individual eyes associated to act together as a synergic whole, but their actions must be controlled as a unit, as if the two eyes were combined in a single central organ. Thus for horizontal deviation to the right the principal actions are those of the adducting muscles of the left eye and the abducting muscles of the right, the two acting as if they constituted a single right-sided mechanism. The reverse is true for left-sided deviation. Movements

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in an upward or in a downward direction also show that the two eyes act as a unit. Besides the actions in the horizontal and vertical planes, there are rotational and other ocular movements. Thus there are the acts of convergence and divergence. Still another, and rarely emphasized, ocular action is eye centering. That eye centering exists cannot be denied. It is manifest during staring straight ahead or on fixation with the eyes at a distance without there being convergence. This eye centering is just as much a patterned conjugate eye movement as is the classic ocular deviation to right or left. Because most studies on eye movements have dealt with the well-known deviations from the center, there is little information on conjugate movement toward the center or on eye centering.

The anatomic and physiologic explanations for the horizontal, vertical, and convergence movements have been amply described. The cerebral and brain stem mechanisms for these are best considered in great detail in the textbooks of Duke-Elder * and Spiegel and Sommer.[3] In general, it is agreed that all eye deviational and vergent movements are influenced by cerebral activity, notably frontal and occipital (visual) impulses, and by brain stem vestibular and tonic neck impulses. There is practically no information on the anatomy, physiology, and pathology of eye centering. Sherrington,[4] in his studies on integrative actions of the nervous system, makes reference to eye centering. He states that following total denervation of the ocular muscles in the monkey the eyes assume a central position. From this it might be inferred that eye centering is simply an inhibitory process, rather than a patterned excitatory process leading to an integrated contraction of various ocular muscles.

Before we consider the mechanism of eye centering, it should be emphasized again that in all ocular movements the eyes remain and act together. One may naturally ask, then, what keeps the eyes together. Is it simply the interaction between the vectors which turn the eyes away from the center, or is there another force superimposed on the deviational vectors which binds the eyes during all types of ocular deviations and in vergence? Is there also a mechanism which centers the eyes, such as one finds in rapid and instantaneous fixation? Is there a conjugate centering reflex when both eyes maintain, throughout all of their excursions and in all positions, a condition of perfect parallelism? The answers to some, if not all, of the questions may be found in the following (I) clinical and (II) physiologic and anatomic considerations.

I. CLINICAL CONSIDERATIONS

A. The Irritative and Paralytic Manifestations of Eye Centering

From a survey of the clinical material one would suspect that there is an eye-centering mechanism. The data may be divided into the irritative and the paralytic aspects of eye centering. Examples of irritative effects may be found in a study of diseases of cerebral and basal ganglia structures.

(*a*) *Convulsive Disorders.*—Eye-centering movements may occur in various types of seizures. For instance, just as irritative lesions of the cerebral cortex, with manifest convulsions, produce tonic or clonic deviations of the eyes in the horizontal or vertical planes, so there are irritative lesions which produce a centering or a staring of the eyes. The clearest example of eye centering is the direct forward gaze or the sudden stare which occurs in petit mal seizures. The same conjugate eye centering may be observed in other types of cerebral episodes, such as at the onset of a grand mal seizure.

(*b*) *Spasms of Ocular Fixation.*—Another example of irritative, or, more accurately, spastic, types of eye centering is found in disease of the basal ganglia. In a study of oculogyric crises there are numerous instances of upward, oblique, and downward, as well as horizontal, ocular spasms. However, there are also sporadic case reports of spasms of fixation and spasms of forward gaze. The earliest description of this observation was made by Gowers in 1879.[5] In

* References 1 and 2.

spasms of fixation the gaze becomes anchored to a visual target so firmly that further ocular movement can occur only if the fixation reflex is abolished by cutting off all retinal impulses. The patient must temporarily close his eyes or cover them with his hand in order to change the posture of his eyes. The spasm of fixation may give the relative appearance of a paralysis of eye movements in all directions. In some of these cases, though the patient fails to move his eyes in one or in all directions on command or to turn them to an object, the eyes at times move about in a more or less normal manner. It is interesting that in cases of partial paresis, voluntary movement may be impossible when fixation is maintained, but if it is abolished by placing a card immediately before the eyes, the patient may be able, perhaps in a jerky and discontinuous way, to move his eyes on command.

Another interesting and significant finding in these cases of spasms of fixation is that on stimulation of the vestibular system (with cold-water irrigation, by turning in a chair, or by galvanic current) there occurs a strong, slow deviation of the eyes, but there is no nystagmus, or at the most a few irregular jerks result. In other words, there was no quick component to pull against the slow deviation induced by the vestibular stimulation.

Thus the foregoing clinical data reveal that irritation of certain regions of the nervous system may produce conjugate centering of eyes, just as certain regions when irritated may produce a variety of conjugate deviations of the eyes away from the midposition, depending upon the site of irritation. The response may be either convulsive-like or spastic in nature. These findings suggest the possibility of the presence of an eye-centering mechanism and that eye centering in these cases is an irritative, and not always an active inhibitory, process.

(*c*) *Paralytic Manifestations of Eye Centering.*—The next question one may ask is this: Will a lesion in these specific regions of the central nervous system which on irritation produce eye centering result in a paralysis of eye centering? What are the manifestations of paralysis of conjugate eye centering?

How does one recognize a patient's inability to gaze directly forward? If the subject is asked to fix a target at a distance or to "look directly ahead," the possible manifestations of such defects in such gaze may be (*a*) deviation of the eyes away from the center of gaze or an inability to fixate (paralysis of fixation), (*b*) nystagmus on forward gaze as a result of conflict between forces which tend to keep the eyes forward and those forces which deviate the eyes to one side, (*c*) abolition of the quick component of induced or a pathologic jerky nystagmus,† (*d*) dissociation of eye movements, (*e*) loss of convergence, and (*f*) inability to hold the eyes together (phorias). The last two will not be considered in this communication.

Paralysis of fixation might be an example of a defect in eye centering. Fixation palsy may occur as a result of lesions in the afferent visual system. Since occipital cortical lesions involve loss of vision owing to the destruction of the afferent visual impulses, disturbances of the fixation reflexes cannot be appreciated in these cases of blindness. It follows, then, that the effects of lesions of the fixation mechanism can be studied only in those rare instances wherein the efferent occipitotectal fibers are involved and both the closely associated optic radiations and the more distantly situated descending fibers from the frontal, temporal, and parietal oculogyric regions are spared.

Gross symptoms seem to follow bilateral lesions only. According to Holmes, in these cases the inability to maintain fixation is complete, with most disturbing consequences.‡ The eyes oscillate about the object of fixation, although there is no true rhythmic or jerky nystagmus. They cannot follow moving objects, and when the patient moves or travels, accurate vision is impossi-

† This statement is based on the theory that the quick component of nystagmus is an expression of eye centering. This matter will be considered in subsequent paragraphs.

‡ References 6 and 7.

ble. The patients cannot "seize" or "hold" objects with their eyes. A line of print cannot be followed. In practice, little or nothing can be seen or focused distinctly, either with one eye or with two. Fusion, accommodation, and convergence may all be deficient. In general, although there is no ocular palsy, nystagmus, or diplopia, there is a total inability to keep the eyes in a position to which they have been brought voluntarily. In essence, although voluntary movement is possible, it is not supported and maintained by the fixation reflex.§

In unilateral cases the symptoms are less pronounced, but difficulty in maintaining fixation may be considerable, and is always greater if the gaze is directed to the side so that more muscular effort is required. If fixation is attempted, particularly with the eyes deviated, it is soon lost and the eyes return to their position of rest, to be brought back again to the object of attention by a series of quick jerks. Similar difficulties are experienced in following a moving object or in fixing a stationary object when the patient's head is rotated or he himself is moving. Fixation can be attained, but its maintenance is difficult. These difficulties may be manifestations of trouble in the eye-centering mechanism.

B. Nystagmus as a Sign of the Presence of an Eye-Centering System

The foregoing clinical data deal with gross disorders of eye centering as a result of alterations in cerebral function. We must now search other parts of nervous system function for evidences of an eye-centering system. Let us, for instance, consider the brain stem with its influence on eye movements, and in particular nystagmus.

Although it may resemble a tremulous or irregular action of the extraocular muscles, nystagmus is a definitely coordinated rhythmic excursion, both eyes moving synchronously over a virtually equal range. It involves not only the rhythmic periodic contraction of certain muscles, but the orderly relaxation of their antagonists by virtue of reciprocal innervation, a coordination which has been demonstrated experimentally by the observation of isolated muscles detached from their insertions in animals and by the records of their action currents.

(*a*) *Vestibular Influences.*—The central mechanism subserving nystagmus consequent to vestibular stimulation has given rise to much speculation. It is universally agreed that the slow ocular deviation outward is peripheral in origin, arising from the labyrinth, the sensory stimuli from these organs being integrated in the structures of the midbrain.‖ The afferent paths for the slow phase in vestibular nystagmus are to some extent known. They are centered around the superior and medial vestibular nuclei. Destruction of the lateral vestibular nucleus does not interrupt the reflex.

The origin of the quick component, moving the eyes backward from the direction of the slow tonic pull, however, has been the subject of much dispute. Although possible, it does not seem to be due to a rhythmic relaxation of the muscles which pulled the eyes to one side. Some of the theories proposed to explain this phenomenon have been summarized by Spiegel ¶ as follows:

Group I. The cerebral theory, which attributes the function to the parts of the central nervous system above the midbrain.

Group II. Theories assuming that the origin of the rhythm is in parts of the vestibulo-ocular reflex arc.

The various theories of Group II may be enumerated as follows:

1. The proprioceptor theory, which assumes that the rhythmic reaction is due to proprioceptive impulses from the ocular muscles.

§ It is noted that, apart from this condition, inability to fix may be the result of (1) defective vision due to lesions of the ocular media, (2) a central scotoma, (3) nystagmus, (4) eye muscle palsy or spasm, or (5) a defect in visual orientation. None of these conditions is present in cases of fixation palsy.

‖ This does not mean that the slow phase of all types of nystagmus originates in the vestibular or brain stem systems. Cerebral and other influences on the slow phase must be borne in mind.

¶ References 3 and 8.

2. The ocular muscle nuclei theory, which locates the origin of the rhythm in the nuclei of the motor nerves to the ocular muscles. The assumption is that there is a mutual inhibition of the oculomotor nuclei.

3. The labyrinthine theory, which seeks the origin of the rhythm in the labyrinth.

4. The vestibular nuclei theory, which attempts to localize the origin of the rhythm in the vestibular nuclei.

5. The reticulate substance theory, which localizes the origin of the rhythm in the substantia reticularis rhombencephali.

None of these theories, however, actually considers the basis of the rhythm. This problem is still unsolved. According to Duke-Elder, the fast phase (the rapid restitutional movement), which is not present at birth or in sleep and is influenced by visual stimuli, is mediated by tracts as yet unknown. In animals it is probably not of vestibular origin and is most likely controlled by "supravestibular centres in the brain stem." But in man, he says, it may be cerebral, mediated through the basal ganglia. Other writers, reasoning from the fact that this phase disappears under deep anesthesia or in deep sleep, have suggested that it is indeed initiated by the cortex. Nevertheless, both Spiegel and Duke-Elder dismiss the cerebral theory on the grounds that both the slow and the quick phase remain intact after extirpation of the cerebral hemispheres [9] or after section of the brain down to the level of the oculomotor nuclei.# And yet we know that the cerebrum does have some influence. After removal of a cerebral hemisphere, induced nystagmus is less when the gaze is directed to the side opposite the lesion and normal or increased when directed to the side opposite the intact cerebrum.[12] The removal of the cerebellar hemisphere also influences induced nystagmus. Some of these hemispheric influences will be discussed in subsequent paragraphs.

According to Spiegel, then, the problem of the origin of the quick component restricts itself to the alternative between the vestibular nucleus theory and the reticular substance theory.

In previous years a reflex center controlling nystagmus in the brain stem has been postulated. Bárány considered that the fast component was of central origin, depending on a hypothetical supranuclear gazing center in the pons.[13] Ohm located it near the vestibular nucleus,[14] and Bartels (1941) in the reticular substance of the pons.[15] According to Bartels,[15] connections are made with the striate nuclei, the hypothalamus, the substantia nigra, the red nucleus, and the dentate nucleus subserving tonic impulses. Other pathways connect with the oculomotor nuclei, the superior colliculi, the vestibular apparatus, and the midfrontal convolution of the cortex. The belief that the quick component is mediated through the reticular substance was proposed by Lorente de Nó * in 1928. He reached this conclusion when he observed that a lesion in the reticular formation abolished the quick component of induced nystagmus. Spiegel and Price,[8] who made similar experiments, observed that the abolition was temporary. Consequently, they differed with the theory proposed by Lorente de Nó and tended toward the "vestibular nuclei theory." In any case most investigators looked toward the brain stem, reticular formation, or vestibular system as the anatomic substrate for the quick component of labyrinthian nystagmus. From a review of the literature, one must conclude that there must be a coordinating mechanism for the eyes situated in the brain stem and it may be more than theoretical.

In connection with this, it is proposed that this mysterious coordinating mechanism in the brain stem is actually a part of the eye-centering system. The eye-centering system is not confined to the brain stem, for, as will be shown later, it is also found to be widely represented in the cerebral hemispheres. This system is integrated at the cerebral and brain stem levels.

(*b*) *Cerebral Influences.* — The importance of impulses from cerebral regions that

References 9, 10, and 11.

* References 16 and 17.

reach the vestibular nuclei, especially impulses from the frontal and occipital cortex, is illustrated by the fact that "voluntary" deviation of the eyes in the direction of the fast component increases the intensity of the induced nystagmus. Moreover, following frontal lobectomy an induced nystagmus with the fast component to the side of the lesion is much more apparent than the nystagmus with the quick phase to the normal side of the brain.† In other words, the intensity of the quick component is decreased by a contralateral cerebral lesion. And, as it will be shown later, a decrease in the visual factors, such as elimination of vision either by abolition of surrounding illumination or by section of the fibers anywhere along the visual systems to both occipital lobes, accentuates and prolongs the induced vestibular nystagmus. Moreover, lesions in the cerebral "optomotor" zones abolish the quick component of opticomotor nystagmus.

It has been claimed that in cortical lesions which result in a deviation of the head and eyes, spontaneous nystagmus does not occur. This is not altogether true, because instances of "cortical fixation nystagmus" due to frontal injury have been reported. I personally have observed several such cases. In fact, the more one searches for fixation nystagmus in patients with cerebral lesions the more cases one finds. These will be described in a separate communication. Gaze-paretic nystagmus may appear in association with impaired ability to look in any particular direction with both eyes. For instance, a patient with impaired ability to turn both eyes to the right or up or down may, by straining, manage to make such a movement to a slight degree; but the eyes will slip back again to the primary, or central, position. This play of alternation between straining to innervate the eyes and their slipping back toward the center appears as a nystagmus. In fixation paralysis the eyes oscillate around the object of fixation but there is no jerky nystagmus.

(*c*) *Opticomotor Nystagmus.*—Another type of ocular movement to consider in which the eye-centering system might play a role is opticomotor, or optokinetic, nystagmus. In this type of nystagmus there is also a slow and a quick component. The eyes follow the stripe toward the side (slow phase) and then jerk back in the opposite direction, toward the center (quick phase). There is a tendency to center the eyes after they have been pulled to one side. Optokinetic nystagmus is a reflex response in which the cerebrum and brain stem are involved. The slow component is said to be visual (cortex or subcortical), but the origin of the quick phase is, again, not easily explained.[19]

It was formerly assumed that the quick component is a focusing movement, called forth reflexly by the object that next appears in the visual field. This implied that the rapid phase was also initiated by the afferent, or visual, system. Such a theory, however, met with a number of objections, the chief of which is that the optic nystagmus remains elicitable even when there are extensive defects in the visual field.‡ In cases of hemianopsia due to lesions of the optic chiasm or optic tract there is no loss of opticomotor nystagmus when either or both eyes are tested. Another objection is that the eye likewise returns with a quick movement to its original position after cessation of the fixation, even when the following movement is elicited by a single object (ter Braak[23]). Then there are instances of after-nystagmus, in which there is a continuation of optically induced nystagmus even in the dark, when the visual stimuli are no longer there. The beat of the nystagmus persists as if there were a spring mechanism which was "wound up" by the rhythmic opticomotor visual impulses. Optically conditioned focusing of a succeeding object therefore plays only a minor role in the mechanism of the quick phase of the optic nystagmus. Kestenbaum[22] considers that the quick component represents the return of the eyes to the intended direction of gaze, actually central fixation.

† References 9 and 18.

‡ References 20 to 22.

In cases with disturbance of voluntary eye movements in one direction, absence of the quick phase of the optic nystagmus in that direction has been observed. From this it may be inferred that the impulse which effects voluntary ocular movements certainly can influence optic nystagmus. Acute destruction of one frontal lobe may abolish optokinetic nystagmus in the direction of the quick component, which direction is opposite the lesion. Strauss,§ however, found that such opticomotor defects are temporary, suggesting that opticomotor impulses must have origin in other areas of the brain.

The frontal lobe is not the only region which influences opticomotor nystagmus. Although voluntary gaze is actuated by the frontal lobe, both components of opticomotor nystagmus may still be produced in cases of bilateral frontal lobectomy. Hence the question arises whether subcortical mechanisms, such as brain stem or, for that matter, other parts of the cerebral cortex, such as occipital, parietal, or temporal lobe, do not play a part in the "jerking back" of the eyes, i. e., the rapid component of opticomotor nystagmus.

There are some who believe that reduction in optic nystagmus to one side has localizing significance. Large visual field defects may lead to a slight diminution of the amplitude and frequency of the optic nystagmus toward the side in question, a fact that is hardly of diagnostic significance. On the other hand, there may be absence of optic nystagmus with or without the presence of homonymous hemianopsia, especially if the lesion has involved the "optomotor area" on the convexity of the occipital lobe or the "optomotor paths" in the lower parietal lobe. It should be borne in mind that unilateral absence of optic nystagmus does not occur in patients with hemianopsia due to lesion of the optic tract, and it is significant that there are no known "optomotor paths" in the tract. In lesions of the "optomotor system" either the quick phase only is absent, or both phases of the optokinetic nystagmus directed to the side opposite the lesion are absent.‖ An interruption of paths that course caudally to the midbrain from the various "optomotor regions" may also yield interrupted "stair-like" movements of the eyes when the patient looks to the side, upward, or downward.[28] These clinical observations suggest that the quick component of nystagmus is influenced by cerebral impulses and that these impulses originate in "opticomotor" zones of the cerebral cortex. This hypothesis should be considered when we examine the data on ocular movement obtained on stimulation of the cerebral hemispheres.

(*d*) *Nystagmus on Forward Gaze.*—While vestibular stimulation will result in a nystagmus even with the eyes in a forward position, defects in vestibular function will not as a rule manifest a nystagmus unless the eyes are voluntarily deviated away from the slow pull. In either instance the nystagmus is made much more apparent when the eyes are deviated away from the midline, in a direction away from the tonic pull or in the direction of the quick component. In contrast to this deviational nystagmus, there is a type of nystagmus which is most apparent on forward gaze and becomes less apparent, or is completely abolished, when the eyes are deviated to one side.

In the first type of nystagmus on forward gaze there is interaction between the flow of impulses from the stimulated or defective vestibular system and the opposing intact forces of the eye-centering system. In other words, the imbalance or the resultant effect between these two opposing forces is a nystagmus. The greater the alteration (irritative or paralytic) in the central vestibular function the more apparent is the activity of the eye-centering mechanism. Also, the stronger the impulses which pull the eyes away from the deviational forces, the more apparent is the nystagmus. Conversely, if the forces which deviate the eyes to the side are much stronger than those of eye centering, then there is decrease in the nystagmus.

In the second type of nystagmus on forward gaze, the imbalance is between a nor-

§ References 24 and 25.

‖ References 26 and 27.

mal deviating force and a defective centering force. In these cases the nystagmus is apparent on forward gaze, and little, if any, nystagmus is apparent when the eyes are deviated. One example of this type of nystagmus is fixation nystagmus, as described in lesions of the optomotor zone of the cerebrum. Another example is the nystagmus on forward gaze produced by a lesion in the eye-centering system of the brain stem. In the latter the nystagmus is more apparent, more enduring, and often occurs jointly with other types of nystagmus.

There are other types of nystagmus which cannot be accounted for by imbalance between deviational and centering forces. The probable explanation for mixed types of nystagmus is multiple lesions—not only in the eye-centering but in eye-turning forces as well. Shimmering, oscillating, slow, wandering, or other types of nystagmus may each have a different underlying single or multiple mechanism. Since the purpose of this thesis is to call attention to the eye-centering system, there is no need to go into a detailed discussion of all types of nystagmus. Such consideration will be made in separate communications.

C. Abolition of the Quick Component of Nystagmus as a Sign of a Defect in the Eye-Centering Mechanism

(*a*) The problem of the impairment or loss of the quick component as a result of lesions in the "optomotor" regions of the cerebrum has already been discussed. This is manifest by an alteration in the quality of induced labyrinthian nystagmus and a loss in opticomotor nystagmus, the loss or defect in the quick component being in a direction opposite the cerebral lesion.

(*b*) Previously it was assumed that the quick component of an induced or a pathologic vestibular nystagmus was the result of interaction between the vestibular deviation force (slow phase) and the eye-centering force (quick phase). The eye-centering force tends to return the eyes toward the center, or away from the vestibular impulses, which pull the eyes to the side. The quick component becomes apparent only when the vestibular mechanism is out of balance as a result of irritation or deficiency. Now if the situation is reversed; that is, if the vestibular mechanism is intact while the centering mechanism is defective or irritated, the reverse will be true. Thus there will be either an abolition (defect) of the quick component or a spasm (irritation) in eye centering. The latter has already been discussed. Again it should be noted that in spasm of eye centering the quick component may be absent on stimulation of the vestibular system. This may be due to strong irritation or activity within the eye-centering system. This, in turn, overcomes any deviational pull exerted by vestibular or optokinetic inputs and thus prevents a nystagmus. Nystagmus is also abolished by lesions in the centering system of the brain stem. The finding of an abolition of the quick component of nystagmus in disease of the paramedian zone of the brain stem is well known. In cases of bilateral paralysis of horizontal conjugate gaze as a result of lesion in the midportion of the tegmentum of the pons, cold caloric stimulation will produce strong deviation of the eyes to the side of stimulation. The deviation will persist, there being no return to the midline. The deviational force is intact, while the centering force is absent. In cases of unilateral paralysis of conjugate gaze, as a result of a lesion in the paramedian zone, for instance, on the right side, stimulation of the left ear with cold water will produce strong conjugate deviation to the left side, there being no quick component to the opposite, or right, side; stimulation with cold water of the right ear will yield deviation to the right, and the quick component to the left will be preserved.

(*c*) Abolition of the quick component of induced labyrinthian nystagmus may also be found when the animal or a patient is under an anesthetic or when the patient is asleep or in coma. This effect is bilateral and in all planes. It has been observed invariably in our experiments on the monkey and in our studies on man. Caloric irrigation in these

instances causes ocular deviation, there being no nystagmus. The quick component is not present. The quick component also disappears in subjects who show a tendency to fall asleep. In experiments with normal monkeys rotational or caloric stimulations produce the usual nystagmus with slow and quick components. However, if the monkey tends to fall asleep during this period, separation of the eyelids shows the eyes deviated to the side of the slow phase and there is no nystagmus—no quick component. On the other hand, when the monkey is awakened with a pinch of the tail, the jerky nystagmus reappears even after the caloric stimulation has stopped. This nystagmus lasts so long as the monkey is awake and the influence of vestibular system stimulation persists.

The abolition of the quick component in opticomotor nystagmus is manifested by a lack of the opticomotor response on stimulation with the rotating striped drum before the eyes. This lack of opticomotor response has been noted in lesions of the frontal, parietal, and occipital, and even temporal, lobe. We have also observed this loss in lesions of the brain stem in man and in the experimental monkey. In the monkey a lesion of the paramedian zone will produce a loss of the opticomotor response. Moreover, the opticomotor nystagmus of a normal monkey will be accentuated when its tail is pinched or it is alerted by any other method.

While all of these observations do not necessarily prove that the abolition of quick component is due to a defect in eye-centering mechanism, the previous clinical data and the subsequent anatomic-physiologic data, which will be brought forth, tend to support the theory that such a centering mechanism indeed exists.

D. Dissociation of Eye Movements as a Manifestation of a Defect in Eye Centering

Eye movements occur coordinately and act together. A defect which may produce a dissociation in ocular movement might be due to a lesion in the central nervous system which has to do with eye centering. This type of ocular defect is most apt to occur in a lesion of the brain stem rather than in the cerebrum. It has been observed that lesions of the brain stem in the paramedian zone not only may cause a loss of the quick component but also produce unequal movements in the eyes, as if the two globes were not being kept together. Repeated observations in man and monkey in whom the quick component was abolished by subanesthetic or anesthetic doses of barbiturates, also disclosed frequent dissociation between the eyes either at rest or in the well-known spontaneous deviations. Moreover, in states of sleep or when there is a lack of alertness there is frequently dissociation between the eye movements. Thus, on horizontal deviation produced by vestibular stimulation there is often an overaction of the adductor, so that there may occur a convergent, or even downward, movement in the adducted eye. At other times there may be divergence of the eyes with slow wandering movements, there being no conjugate action throughout this period. These dissociations have been frequently observed in cases of coma in which eye movements were induced either by vestibular stimulation or by head turning. In other words, in all of these instances there is a lack of influence which keeps the eyes together, and in all of these instances there is no quick component. It is possible that the lack of eyes being kept together and the lack of nystagmus is each due to a defect in the eye-centering mechanism. This double manifestation of defect in eye centering is sometimes seen in another form in the awake or alert organism. There are case reports of dissociation in conjugate eye deviation as well as in nystagmus.

II. PHYSIOLOGIC AND ANATOMIC STUDIES

From the foregoing clinicopathological considerations one might postulate a mechanism for eye centering, the efferent pathways of which are situated in the cerebrum and project down into the brain stem. In the midbrain and pons these pathways are situated in the paramedian zone in close

proximity to the oculomotor nuclei. The function mediated by these pathways is to coordinate the movements of the eyes and keep them in the center in relation to the head. Such a mechanism acts at higher physiologic levels than the primary oculomotor nuclei, and deals with the more complex associational or coordinating activity which mediates vertical and lateral conjugate movements, as well as conjugate centering of the eyes. It would appear that such an activity is also carried out by pathways in the frontal, parietal, temporal, and occipital eye fields and by intermediary pathways situated in the brain stem. The integration of this action takes place continuously at various levels from the cerebrum to the medulla. Such cerebral and brain stem systems might be inferred from clinical observations made on the derangements of eye-centering function.

A. Cerebral Studies.—Clinically it has been observed that the fixation reflex of eye centering has been defective in cases of lesions of the dorsal portions of the thalamus, including the pulvinar, and in cases of lesions of the occipital lobe. According to Holmes,[7] postmortem evidence has shown that defects in the fixation reflex, even though vision is preserved, is "due to interruption of the cortico-tectal fibers which form the efferent limb of the reflex arc. . . . In a few of the recorded cases there were bilateral injuries of the frontal oculomotor centres but more commonly the projection fibers from these centres were involved in the internal capsule or caudal to it."

Thus the clinicopathologic evidence only suggests an anatomic basis for the fixation reflex, and possibly eye centering. However, one might consider here the old and recent studies which dealt with eye centering and stimulation of the cerebrum. In 1886 Ferrier,[29] in his experiments on stimulation of the brain, made reference to the phenomenon when he described the appearance of the eyes as one of expression of attention or surprise. Subsequently, Beevor and Horsley,[30] in 1888, Mott and Schaefer,[31] in 1890, and, recently, our own experiments in monkeys have shown that electric stimulation of specific regions in the frontal, occipital, parietal, or temporal lobe cortex produced a bilateral eye centering. This eye centering has been called (*a*) "awakening response" by Smith[32] (1949), (*b*) "the orientation of the optical axes reflex" by Brown[33] (1922), (*c*) centering the eyes by Chusid, Sugar, and French[34] (1948), and (*d*) "mid-positioning of eyes" (1949).[35]

The functional interdependence of the cortical oculogyric reactive zones and the influence of other cortical areas upon their activity were experimentally studied by Claes.[36] He found that cocainization of one occipital opticomotor region increased the electrical excitability of the other, indicating a mutual inhibition of the left and the right side. However, such a mutual relationship between the left and right frontal eye fields could not be found. One of the functions of the frontal areas consists in bringing the deviated eyeballs into the position of "static equilibrium" and keeping them in this position during attention. If, for instance, the eyes are deviated by electric stimulation of an occipital focus, stimulation of the homolateral frontal region brings the eyes into equilibrium position. This has been attributed to an inhibition of the activity of the occipital zone, whereas actually it may be due to activation of the cerebral eye-centering system. Moreover, subthreshold stimulation of the posterior area slightly increases the excitability of the homolateral frontal one. Depression of the activity of the area striata by cocainization lowers the excitability of the anterior and posterior oculogyric foci without affecting the excitability of the other motor cortical regions, demonstrating the influence of sensory impulses upon the activity of the oculogyric zones.

It must be assumed that the excitable cortical areas which on stimulation yield ocular deviation, as well as eye centering, are projected down toward the brain stem. At present we are in the process of tracing these pathways electrically through the subcortical regions with the aid of a stereotaxic instrument. Incomplete studies have revealed

that almost from every focus which electric stimulation yields conjugate eye deviation one may also elicit an eye-centering movement.[37] This implies that fibers mediating ocular centering and ocular deviation are either (*a*) separate, but intimately in contact with each other, or (*b*) the same fiber system conducts all types of ocular movements but each type, such as centering or deviation, is activated by different forces. Another interesting observation in these preliminary studies on subcortical pathways for eye movements has been made in the unanesthetized monkey which had a cervical transection. Such a monkey is wide-awake and follows visual targets very readily. Stimulation of the brain in this preparation results in eye centering, even though the monkey attempts to follow a peanut or raisin with its eyes. In fact, if the stimulation is continued, there develops an oscillation between the slow horizontal deviation of the eyes created by the visual target (food) situated to one side and the continued electrical stimulation which snaps the eyes back to the center. The result is a jerky nystagmus with a slow (deviational) and quick (centering) phase.

On correlation of the foregoing experimental data on the cerebrum with the clinicopathologic studies on the brain in man, the theory that an eye-centering mechanism exists in the brain is somewhat strengthened. Since the theory also states that an eye-centering system operates in the cerebrum down to the vestibular and oculomotor nuclei, one must consider experiments on the pathways through the brain stem.

B. Brain Stem Studies

In clinicopathologic studies of the brain stem it was noted that lesions in the paramedian zone of the tegmentum of the upper medulla, pons, or midbrain produced an abolition of induced nystagmus. Labyrinthine stimulation produced only an ocular deviation to one side. There was no quick component. These same patients and experimental animals also showed no opticomotor reactions. Applying the theory that the quick component is but one manifestation of an eye-centering system, we might reason that the paramedian zone is the anatomic substrate for the mediation of this mechanism at the level of the brain stem. In support of this deduction one may cite the experimental observations on the brain stem of the monkey.

Recent anatomic and physiologic studies have shown that electric stimulation of foci through the entire paramedian zone of the tegmentum of the brain stem extending from the upper medulla and pons to the midbrain and pretectal region, as well as some parts of the colliculi, periaqueductal gray matter, and parts of the vermis of the cerebellum, results in a distinct centering of the eyes.[38] There is no experimental evidence that ocular centering is integrated within the superior colliculus, as proposed by Pitts and McCulloch.[39] The eye centering observed on electric stimulation is prompt, bilateral and can be elicited with very small currents. Ocular centering has also been noted in regions in which stimulation may also yield a variety of uniocular and binocular excursions. In some regions the two types of eye movements (deviational and centering) can be obtained from the same anatomic point with the same current; the eye centering often precedes the conjugate deviation, or if one eye moves in any one direction the other eye is "centered." Also, if the frequency or the strength of current is varied, only one type of movement may occur.

In studying the effects of lesions in the paramedian zone of monkeys, we found that the results coincide with clinicopathologic studies of the brain stem in man. Even though our clinical and experimental data are incomplete, the facts show that some, but not all, lesions in the paramedian zone of the tegmentum of the brain stem abolish the quick component of vestibular or optokinetically induced nystagmus. In general one must conclude that stimulation of the paramedian zone of the tegmentum produces eye centering, while lesions in some of these regions cause an abolition of the quick component of nystagmus. In correlating the two

sets of data, one might suppose that the abolition of the quick component of nystagmus is a defect in the eye-centering mechanism.

C. Relation Between Eye-Centering Mechanism and the "Activating" System

Magoun and his co-workers¶ postulated an activating or awakening system which pathways were situated in the paramedian zone of the brain stem. Electric stimulation of one focus in this area of the brain stem produced electroencephalographic changes in both cerebral hemispheres, most marked in the frontal leads. This was interpreted as an arousal or awakening reaction. Since stimulation of the same region produces eye centering, one might suspect that this type of oculomotor response is also part of an alerting or waking pattern. There is no denying that eye centering participates in the awakening response, but one must not overlook the fact that eye centering occurs in other types of total body reactions, such as central fixation of a target and in body righting movements. Thus if an object is viewed by a subject, either the eyes or the head and neck are so turned that the eyes appear to be centered. This type of ocular behavior may have something to do with alertness, but then any movement may be interpreted as a response of alertness.

Since it has been postulated that the quick component is an expression of activity of the eye-centering system, it follows that a loss of activity of this centering system would abolish the quick component of ocular nystagmus. Moreover, if the eye centering is intimately related to the awakening or alerting system, it would also follow that a decrease in the awakening state would produce a decrease in eye-centering activity. This is what actually happens. Pathologic nystagmus or nystagmus induced by vestibular turning or caloric stimulation is immediately abolished when a monkey falls asleep. Contrariwise, as soon as the monkey is awakened by such stimuli as loud noise or pinching of its tail, the nystagmus reappears. This disappearance and revival of the nystagmus can be observed invariably in any monkey which happens to have a nystagmus with a quick component, whether it be pathologically or physiologically induced. It should be noted here that the quick component of nystagmus induced by caloric or turning stimulations is also abolished by intravenous injections of amobarbital (Amytal); the response to vestibular stimulation is deviational, so that the eyes turn to one side. There is no centering phase. A second example in which the quick component is abolished is the effect of amobarbital sodium on opticomotor nystagmus. With small doses of this drug there is no longer opticomotor response, even though the subject is only partly drowsy.[42] A third example is the abolition of nystagmus on forward gaze even with small doses of barbiturate.[43] In all of these instances, namely, natural or induced sleep or lack of alertness of varying degrees produced by drugs or other conditions, there is an abolition of nystagmus or a disappearance of the quick component or a "deactivation" of the eye-centering system.

In conjunction with some of the foregoing observations, Wendt # uses the term "habituation" to vestibular stimulation in cases in which nystagmus disappears as a result of a lack of "alertness." This term was derived from the researches of Dodge.[46] Wendt says there are two factors in "habituation," which may be present separately or together: one in which visual stimuli tend to inhibit the vestibular nystagmus, and with repetition these stimuli become increasingly dominant. The other factor is lack of alertness. This form of habituation with loss of nystagmus (even when the eyes are closed) can be prevented by keeping the subject attentive to external environment and "avoiding" inward-directed revery states. From studies made on man and monkey he believes that "habituation" occurs as a competition between the vestibular reflex and "another system of control of the eyes." The latter system consists of "an autogenous

¶ References 40 and 41.

References 44 and 45.

wandering of the eyes in a non-conjugate manner such as has been described in states of sleep, unconsciousness or coma. The reflex (vestibular) and this system compete for control in an almost either-or fashion. There are usually sharp, bilaterally, simultaneous transitions from reflex to wandering movement and from wandering movement to reflex."[44] This theory is an attractive one, but its weakness lies in the use of terms. There is no doubt that during the period of a lack of alertness the eyes are influenced in a positive or a negative way (*a*) by a basic system of forces which will abolish the nystagmus, as proposed by Wendt, or (*b*) by a lack of influence, there being a loss of the forces of eye centering, which loss would, in turn, abolish the quick component. It would seem that the latter is the more likely explanation, because sleep or lack of alertness is identified mostly with a decrease, rather than an increase, in activity. While it is true that a subject asleep or under anesthesia may exhibit rhythmic, slow, wandering movements of the eyes, it is improbable that these movements alone would serve as a general explanation for abolition of quick component of nystagmus.

D. Eye Centering and the Righting Reflexes

The tendency of eyes to move toward the center might also be one example of the numerous reflexes which exist in the body righting mechanisms. As a rule the eyes are centered in the normal subject. That is, the eyes are centered in relation to the head. No matter what position they may have assumed, the eyes ultimately move toward the center. Any deviation of eyes from the center causes a continuous tonic pull on the neck and upper trunk. Thus on turning the eyes to the right, such as may occur in fixation of a target, the head and chin tend to turn to the right, so that the eyes are ultimately centered. The ocular fixation reflex and eye centering are intimately related to the head and neck movements. A defect in ocular deviation is often accompanied by a tonic deviation of the head. The tonic deviation of the head is away from the side of the defective eye pulling. It is possible that some of the righting reflexes attributed to the vestibular or visual systems might really have been manifestations of the eye-centering system.

SUMMARY

The suggestion is made that there is a mechanism which centers the eyes. Just as there are mechanisms which turn the eyes away (deviational) from the center, so there seems to be a system which brings them back to the center (centering).

Clinical examples of activation of the eye-centering system are (*a*) grand or petit mal seizures during which the eyes are centrally placed or stare straight ahead, and (*b*) spasms of central fixation, as observed in patients with disease of the basal ganglia, or in patients with postencephalitis, who also may show oculogyric crises.

Clinical examples of a paralytic effect in the eye-centering system are difficulties in central fixation and the fixation nystagmus one finds in bilateral cerebral lesions.

The experimental evidence for an eye-centering system may be found in studies of various cerebral opticomotor regions. Electric stimulation of foci in the frontal, occipital, parietal, and temporal cortex or stimulation along the projected subcortical pathways results either in ocular deviation or in eye centering. The two principal ocular responses may be obtained from the same focus in many regions of the cerebrum. This suggests that these fibers which mediate ocular deviation and centering are in intimate contact with each other, or may even be identical in their course from the cerebrum to the brain stem. Ocular centering may also be obtained on electric stimulation of points in the entire paramedian zone of the tegmentum of the brain stem. Here there must be two sets of fibers, the smaller portion conducting deviational and the larger portion conducting centering movements.

Another clinical manifestation of activity of an eye-centering system may be found in the nystagmus which has a slow and a quick phase (horizontal, vertical, and rotational). The slow phase is due to deviational forces

induced by vestibular or optokinetic stimuli, while the quick phase is due to a hypothetical centering system. This theory does not explain other types of nystagmus.

Experimental and pathologic lesions in the structures which mediate eye centering may result in abolition of the quick component of nystagmus. The quick component of opticomotor nystagmus is abolished or lessened, while that of vestibular nystagmus is lessened by lesions in the opticomotor zones of the cerebral hemispheres. Lesions in the paramedian zone of the tegmentum of the brain stem may abolish the quick component of opticomotor as well as the vestibular induced nystagmus. In summary, lesions along the fiber system which on electric stimulation produces eye centering will result in a decrease or an abolition of the quick component of nystagmus.

The quick component is also abolished during decreased alertness, in sleep, in induced states of narcosis, and in coma. The quick component is revived with consciousness and alertness.

During these altered states of consciousness there is also a dissociation in eye movement, reflecting the lack of a force which keeps the eyes together and centered.

The eye-centering system is in equilibrium with the conjugate deviation system, and these, in turn, are constantly influenced by visual, vestibular, proprioceptive, and somatosensory systems. There is also a relation between the eye-centering system and the alerting mechanism postulated by Magoun and his co-workers.

It is conceded that this theory will not solve all the problems which may be encountered in the study of ocular movements. Nevertheless, the use of this theory has yielded results as predicted, and in some instances new data were obtained. Whether this hypothesis will withstand future tests remains to be seen. At least the concept of eye centering serves an an avenue for investigation of eye movements, and it is expected that more valuable and new data will be gathered by means of this approach.

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A Preliminary Note on the Use of Chlorpromazine with Neuropsychiatric Disorders

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Psychiatric history is replete with many and varied claims of a pharmacological cure for mental diseases. However, few of these claims have withstood the test of rigorous experimentation. Probably the outstanding form of this type of treatment in use today is insulin. However, this treatment has its drawbacks in the form of expense, time, and the necessity of constant supervision. Various drugs, such as the barbiturates, have been used to quiet actively disturbed patients, as has electric shock and hibernotherapy.[3] All of these forms have their liabilities in requiring constant supervision or in leaving the patient in a comatose state for varying periods and, as a result, less accessible than before administration. The lack of accessibility following these accepted treatments is probably the main criticism to be leveled at them. The treatment quiets the patient temporarily but prevents any immediate further treatment in the form of psychotherapy and does not preclude exacerbation.

Chlorpromazine is a recent drug that promises the benefits of present treatments, but apparently without many of the liabilities. Its physiological effects are well described by Lehman and Hanrahan.[1] This paper is a preliminary note on research with this drug now in progress at this hospital.

From the Veterans Administration Hospital.

Mr. J. W. Moyer, physical therapist, gave assistance in this study.

Chlorpromazine was put into use on June 17, 1954, with patients who were exceptionally hyperactive, agitated, and disturbing to the other patients. As customary in this psychiatric hospital, the above-described patients usually received hydrotherapy in the form of neutral wet packs, provided there were no contraindications.

Theoretically, since chlorpromazine has a depressive action on the central nervous system and, as a result, lessens psychomotor excitation, it would be expected that the effects of the drug would be manifested in the number of admissions for wet packs.

The two wards housing the most actively disturbed patients were selected for this study. The number of patients admitted to the respective hydrotherapy rooms of each ward were determined for the 30 days prior to June 17, 1954, and for the 30 days subsequent to this date. It is repeated that chlorpromazine was put into use on June 17, 1954. The drug was administered to a few select patients; for example, only 12 patients of the several hundred that had access to the H ward hydrotherapy room were administered the drug. The average dose was 25 mg. parenterally or 50 mg. orally. This is below the average dose usually reported for NP patients.*

For the 30 days prior to use of chlorpromazine 82 patients were admitted to the H ward hydrotherapy room. Only 48 patients were admitted after use of the drug was instigated. On the O ward, the number of admissions for packs for the two periods was, respectively, 296 versus 206. A "*t*" test was performed on the above data. For the

* References 1 through 3.

H ward the results were significant at the 0.01 point, or a drop in admissions of this magnitude could be expected to occur by chance only once in every hundred times. For the O ward the results were significant at the 0.02 point.

On the basis of the above, it is obvious that the number of admissions to the two pack rooms differed significantly for the two time periods. Since the only difference in treatment that occurred before and after June 17, 1954, was the use of chlorpromazine, we may conclude that this difference was due primarily to the effect of the drug.

However, as an added check on these results, the number of admissions to the two pack rooms for the same periods of time, but one year previously, was determined. The combined number of admissions to the two hydrotherapy rooms for 30 days prior to June 17, 1953, was 742; for the 30 days following the above date the number was 739. There was a difference of only three in the number of admissions. As can be seen, no significant difference existed between these two periods.

It should be noted that the absolute number of admissions is twice as great in June, 1953, as in June, 1954. This drop was due to a change in policy and occurred in the fall of 1953. For the period involved in this study the number of admissions to the hydrotherapy rooms was stabilized at the lower figure. However, this does not detract from the relative differences for the two periods. In 1953 the difference in number of admissions between the two periods was 3; in 1954 the difference between the pre- and the post-drug period was 124.

The above data suggest that chlorpromazine is an effective treatment for calming agitated, severely disturbed, and disturbing patients. While only 12 patients were administered the drug, there was a drop of 34 admissions to the hydrotherapy room for packs. By alleviating the emotional tension in a small number of patients, it was possible to prevent outbursts in others. The effect one disturbed patient can have on others is a well-known clinical phenomenon and is observed in these groups presented here.

At present two additional studies are in progress at this hospital. One study deals with chlorpromazine, and the other with a Rauwolfia serpentina extract. In both studies the effect of the drug in conjunction with group psychotherapy is to be studied, as well as such modalities of therapy as neutral wet packs.

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Society Transactions

NEW YORK NEUROLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY

Joint Meeting, Feb. 8, 1955

E. Jefferson Browder, M.D., *President, New York Neurological Society, Presiding*

Value of Radiation Therapy in Management of Glioma of Optic Nerves and Chiasm.

Dr. Juan M. Taveras (by invitation), Dr. Ernest H. Wood (by invitation), and Dr. Lester A. Mount.

Primary tumors of the optic nerves and chiasm are encountered infrequently, with the result that the effect of various forms of treatment is difficult to evaluate. In the past, emphasis has been placed upon surgical treatment, and there is very little indication from the literature as to how important radiation therapy may be in the management of such neoplasms.

Preliminary observations in the results of treatment of 34 patients with optic nerve glioma at the Neurological Institute of New York and the Institute of Ophthalmology indicate that roentgen therapy is of foremost importance in the control of optic nerve glioma, particularly when combined with conservative surgical treatment. Radical surgery usually results in permanent destruction of the optic pathways or in an increase in the visual deficit caused by tumor. Radiation therapy, in some instances, has resulted in a restoration of vision, while on other occasions advancing impairment caused by the tumor has been arrested. In some of the patients with exophthalmos, the globe has receded completely and permanently. Large tumor doses often are not necessary to produce beneficial effects. The best results have been observed when radiation therapy has been used as the primary method of treatment and surgery has been reserved for those cases in which there is obstruction to the flow of cerebrospinal fluid or in which an existing exophthalmos fails to respond to radiation therapy.

DISCUSSION

Dr. Lester A. Mount: There are a few points which I should like to emphasize. First, surgical therapy is indicated in those cases in which a positive diagnosis cannot be made. This includes the cases in which the tumor is entirely intracranial, having no enlargement of the optic foramen and no exophthalmos. In these cases exploration is indicated to verify the presence of the tumor before starting x-ray therapy, but if the tumor is found to be entirely within the optic chiasm and the optic nerves no biopsy tissue should be taken. In one case in which I operated eight years ago, the patient's only present visual impairment I believe to be the result of the biopsy tissue which I took from his chiasm.

Indication for surgery includes also the cases in which the tumor is entirely within the orbit, with exophthalmos and no enlargement of the optic foramen. Surgical treatment in these patients is an intraorbital exploration before x-ray therapy is started, and if the tumor is found to be within the optic nerve no biopsy should be done.

Operative therapy is necessary in the cases in which there is an obstructive hydrocephalus before x-ray therapy is started. A by-passing procedure is the treatment of choice, as the direct attack on the tumor in an effort to relieve the obstruction usually proves fatal.

A further possible indication for surgery is the case in which the tumor is entirely within the optic nerve. However, such a course would result in the loss of vision in one eye, and it is doubtful that the tumor would grow beyond the point where it could be removed completely in the 28 days necessary to administer 4000 r of x-rays and two weeks thereafter. The patient could then be reevaluated, and if he had not improved, operative therapy would then be imperative.

Dr. George H. Hyslop: As some of you may know, Russell Meyers, of the University of Iowa, has an interest in semantics. At Memorial Hospital some of these tumors which you call optic nerve gliomas are now known as retinoblastomas. When we find it is a retino-

blastoma, it is too late for x-ray treatment, so far as we know now. One of the problems of the so-called optic chiasm glioma, and you can make the diagnosis on the basis of a proper history, excluding a retinoblastoma and excluding x-ray abnormality, is whether it is radiosensitive.

Diurnal Rhythm in Epilepsy. DR. MAX LEVIN.

Epileptic fits do not occur at a uniform rate throughout the day and night. On the contrary, they show a preference for certain hours; these are the late hours of sleep and the early hours of the morning after waking up. The reason for this would seem to lie in the interplay of excitation and inhibition. Excitation and inhibition are constantly counteracting each other, as though in an unceasing struggle. Of course, sooner or later inhibition is "victorious," for sleep (an inhibitory state) is inevitable. At the end of the day excitation has, so to speak, exhausted itself and inhibition takes over. But after a few hours the position is reversed: During sleep the potential for excitation builds up till it reaches a peak when we wake up, ready for the new day. The cycle is like a Ferris wheel that spins once a day. At the start of the day the potential for excitation is at a peak; at the end of the day it is all the way down. The epileptic fit is an excitatory phenomenon, and is therefore more likely to occur in those hours when the potential for excitation is highest.

DISCUSSION

DR. LEO L. ORENSTEIN: The author, by presenting his material, develops his theory of "excitation and inhibition." Dr. Levin even makes use of his understanding of football to illustrate his clinical observations. I like football very much, and if I felt it could enrich my insight into clinical problems, I should attend more games.

There is one disturbing clinical problem, namely, the patient suffering from depression, who frequently is not able to sleep. This patient at the same time shows ample evidence of inhibition of motoric and mental functioning. If in terms of the theory presented tonight excitation leads to activity and fits, and inhibition to a state of sleep, as in narcolepsy, I wonder if the author would care to comment on the paradoxical findings in the patient with depression.

DR. MAX LEVIN: I won't try to answer the question raised by Dr. Orenstein. The problems of depression are infinitely more complex than those of narcolepsy and epilepsy. These last two disorders are relatively simple, and their manifestations can be accounted for by the principles of excitation and inhibition. The problems of depression are of a much higher order of complexity.

Hospital Treatment of Anorexia Nervosa. DR. JAMES H. WALL.

This study was concerned with practical experience in the hospital treatment of 10 patients suffering from anorexia nervosa. The pertinent literature was reviewed. The family background, personality development, and symptoms of the patients were presented.

Little has been added to our understanding of the syndrome since it was described by Sir William Gull, in the last century, but there has been an increase in the study of the condition, paralleling the revival of the interest in psychosomatic disorders. The 10 patients, girls and women, were between the ages of 16 and 38. They moved from one level of adjustment to another with great difficulty and feared growing up and assuming the responsibilities and privileges of adulthood. They repudiated life and sexuality, and the themes of denial and renunciation became most prominent at the time of puberty. As a group they were restless, but shallow, withdrawn, and infantile. This group resembled the sweeping total reaction of simple schizophrenia. Treatment included tube feeding, ambulatory insulin therapy, electric shock therapy, psychotherapy, and socialization through the various program therapies. This group made rather limited adjustments after prolonged periods of treatment. Seven of the 10 have done well, but they continue to be underweight, and all find it difficult to achieve a weight over 100 lb.

DISCUSSION

DR. M. RALPH KAUFFMANN: We, at the hospital, have been interested in the problem of anorexia nervosa, for a number of reasons. One is that the syndrome has remained essen-

tially unaltered since its description by Sir William Gull, in 1873. There are now about 400 papers relating to anorexia nervosa in the literature, and essentially the syndrome remains as originally described. There have been many attempts to explain the syndrome; in recent years there has been an emphasis on certain psychodynamic aspects of the clinical syndrome. All workers have emphasized that in the psychiatric picture one can make, or does make, diagnoses as varying as hysteria, compulsive and obsessive neuroses, schizophrenia, manic-depressive psychosis, and so on; nevertheless, the central elements of anorexia nervosa are the same. It seems as though what one deals with is a syndrome that has a certain specific pattern in a matrix which can be anything from schizophrenia to hysteria. The difficulty in making a diagnosis in any given case as from one hospital to another is rather well known. It is not because one hospital knows how to make the diagnosis and the other does not, but because we deal with a series of defensive maneuvers that are in a dynamic flux and may change at any point in time.

It does seem a little peculiar that none of Dr. Wall's patients should have had any oral impregnation fantasies, since all 24 of the patients that we have had had fantasies of oral impregnation that were so clear-cut that we rather took it for granted.

Dr. Oskar Diethelm: In the 45 patients who were studied at the Payne Whitney Psychiatric Clinic, there have been various groups, including schizophrenic reaction, hysterical reactions, characterized by phobic "anorexia," and compulsive symptoms. It was of interest to me, in going over our material, to note that the least desirable results were obtained in patients who were under 17 years of age. They comprised about 20% of our patients. With two exceptions, they all had a compulsive type of anorexia nervosa but seemed to belong, with those two exceptions, in a schizophrenic entity. I think they were all sent to boarding school or special schools, but with a rather disappointing result. In the cases which Dr. Wall discussed, one of our former patients was included. Good results were obtained in the hysterical reaction of the phobic type of anorexia nervosa in our patients over 20 years of age. In the follow-up study, some including 15 years' duration, the results were good. In these cases long-term psychotherapy was carried out; one patient stayed 14 months in the Clinic for intensive psychotherapy. A certain group included patients who had a compulsive type of food refusal. The outcome was rather interesting. One or two may have had paranoid schizophrenia; others developed rather simple deterioration, some in the hospital, some outside; one received lobotomy, and, as was anticipated, without much benefit.

Newest Trends in Forensic Psychiatry. Dr. Gregory Zilboorg.

The influence of psychiatry has made itself felt in the handling of medicolegal problems of a psychiatric nature. This influence is reflected in such matters as "lie detectors" and various drugs which came into medicolegal practice via the so-called narcoanalysis or narcosynthesis. The crucial question in such matters is whether or no the physiological and/or pharmacological tests are of really evidential nature. No one denies the psychological importance of these measures, but it is questionable whether the amobarbital (Amytal) or thiopental (Pentothal) test is in any way admissible from the purely legal or moral point of view. After all, a person under the influence of a drug is an altered person, and therefore is not the same as the one who committed the crime or who happens to be under consideration. The Yale medicolegal unit does interesting work on this subject, but its conclusions are far from definite or convincing as yet.

The second aspect of psychiatric influence on forensic psychiatry is reflected in the recent decision of the Monte Durham case by the U. S. Court of Appeals of the District of Columbia. This decision is identified with Judge Bazelon, who wrote the opinion, with Judges Washington and Edgerton concurring.

The major feature of this decision is that it does away with the right and wrong test, with the irresistible impulse theory, and, in general, with the purely legal definition of so-called insanity. Instead, it establishes the sound principle of psychiataric criteria and asks the psychiatrist to tell the court and the jury whether the given crime is a direct result of the given mental illness or the given defendant. This is a tremendous advance, but it has its pitfalls in that it throws even a greater burden on psychiatry. However, it has the enormous advantage over the old McNaghton rule in that it eliminates the double standard of insanity—legal and medical—and also frees the psychiatrist from passing on the question of criminal responsibility, which is not a psychiatric question.

PHILADELPHIA PSYCHIATRIC SOCIETY

Manuel Pearson, M.D., President in the Chair
Regular Meeting, Feb. 11, 1955

Use of Chlorpromazine (Thorazine) and Reserpine (Serpasil): Symposium

DR. MANUEL PEARSON, Chairman: The purpose of this meeting is to collect and review our experiences in this area with the use of two new and much discussed drugs, chlorpromazine and reserpine. The program has been planned to include clinical psychiatric observations from our local hospitals and comments from other special fields, such as pharmacology and internal medicine. First, we shall hear the clinical presentations.

DR. JAMES EWING: Out of a small group of similar cases at the Functional Clinic of the University of Pennsylvania, one case of agitated involutional psychosis is presented in detail, in which it is shown that chlorpromazine in doses of 50 mg. four times a day produced a decrease of psychomotor tension and a diminution of suspiciousness and anxiety, with liberation from preoccupation with delusions and, consequently, improved socialization. These trends could be reversed by emotional stress or by decreasing the medication.

DR. EDUARDO D. MALDONADO: The work I shall report was done at Friends Hospital, with the collaboration of Dr. A. O. Hecker. The report consisted of a subjective analysis of the effects of chlorpromazine, based on my personal experience, as well as comments on the treatment of psychotic patients in this Hospital. My personal experiment consisted in taking chlorpromazine by mouth in doses of 50 mg. every four hours for five days. The initial effects became apparent in 15 minutes and progressed for at least 4 hours. No change was observed in perception, memory, or voluntary control of behavior. On the other hand, apperceptive processes were reduced; affectivity was dulled and replaced by a feeling of well-being, or at least of indifference, and the stream of thought, while it remained continuous, coherent, and relevant, was constricted. Late side-effects included tremor, incoordination, tachycardia, dyspnea, irregular pulse, and precordial distress on exertion, associated with a fall in systolic and a rise in diastolic blood pressure, constipation, and polyuria.

We have used chlorpromazine in the treatment of a number of acutely psychotic patients with various diagnoses and have established the following routine: Patients are kept in bed until blood pressure levels have been established, then started on 200 mg. of chlorpromazine intramuscularly every four hours until full clinical effects are obtained. At this point they are shifted to oral doses of the same amount for three days; the dose is then reduced to 200 mg. three times a day for six days, then to 100 mg. orally three times a day, and finally to 50 mg. three times a day "indefinitely." The complications of jaundice, pyrexia, hypotension, tremor, and incoordination were never serious and were readily solved by stopping the drug. In a few instances the medication appeared to work paradoxically, producing depression or an exacerbation of symptoms. The only contraindication to the use of chlorpromazine in our experience is liver damage or active cardiovascular disease. In general, the drug is safe, and its use makes it possible to handle in a general hospital cases which previously required a psychiatric institution.

DR. MANLY BRUNT: At the Pennsylvania Hospital, 44th St., we have treated approximately 50 patients with chlorpromazine in doses up to 800 mg. per day, and about 40 with reserpine in doses up to 10 mg. per day. One patient on chlorpromazine therapy developed hepatitis, and one receiving reserpine, cerebral thrombosis. With reserpine, apathy, drowsiness, and vertigo were common, and diarrhea was an occasional side-effect. It is our impression that both reserpine and chlorpromazine have a mild sedative action, that the action of reserpine is more consistent, and that both drugs have a rather limited use in the treatment of a few selected patients.

DR. FRITZ A. FREYHAN, Farnhurst, Del.: My discussion is based on clinical observations on 250 psychiatric patients hospitalized at the Delaware State Hospital at Farnhurst, Del., who were treated exclusively with chlorpromazine or reserpine, and on comments made to me by colleagues in Germany, Switzerland, and England during a recent visit. The drugs leave consciousness and ego functions intact, but facilitate cortical inhibition and decrease conative intensity, so that harmonization of the personality is accomplished often to an astounding degree. From this, it follows that the drugs are useful only in clinical states that express themselves in hypernormal initiative, and, contrariwise, that they are not effective

in conditions characterized by loss of initiative or apathy. Clinically, manic-depressive patients in the manic phase showed the most satisfactory response; many acute catatonic and paranoid schizophrenics improved, and a few senile patients and patients with central nervous system syphilis and other encephalopathies also benefited.

We have had favorable experiences in treating acute states of alcoholic intoxication and in the management of withdrawal symptoms in drug addicts. The doses used are essentially those described. In Europe, patients are placed on a "hibernation regime" in dark rooms for weeks or months, a practice we have not followed. We distinguish inconsequential "side-effects," such as mild dermatitis, brief periods of hyperthermia, a variety of autonomic dysfunctions, and Parkinsonism, all of which do not necessitate interruption of treatment, from such "complications" as jaundice, toxic reactions, and paradoxical psychological responses, which call for prompt termination. Those complications seem less frequent in Europe than here.

Our experiences with reserpine are still limited, but we are convinced that it is less effective in bringing about rapid control of acutely disturbed patients. Doses of 10 to 20 mg. a day are required. The beneficial results of chlorpromazine may be summarized in administrative terms as marked improvement of the social climate of the psychiatric hospital by change in the chronic disturbed wards; and in terms of the individual patient and therapist as immediate, dramatic transformation of disturbed patients into calm and socially adapted persons and the maintenance of inner experiential continuity, making psychotherapy practical.

Dr. Herbert Freed: The following observations were made in cases at Roseneath Farms, where chlorpromazine was used with 150 patients and reserpine with 25, as well as with 50 private patients and 30 children treated at the Child Psychiatry Clinic of the Philadelphia General Hospital. The adult cases included all types of psychoses, drug addictions, and neuroses, and the children were essentially hyperkinetic and emotionally disturbed. The children's group is controlled, and with chlorpromazine showed an improvement rate of 80%, with no significant complications. In the adults the results were less spectacular, but also good. We do not know the optimal dose of either drug, but they should be larger than originally suggested. The side-effects of chlorpromazine are more marked than those of reserpine—2% of our patients developed jaundice; skin eruptions occurred in 5%, and skin sensitization developed in two of three staff members who handled the drug, while with reserpine, nasal congestion, dizziness, and nausea, all of mild degree, occasionally occurred. On the basis of these studies, I should like to suggest further evaluation of the drugs in combination, and possibly with such other drugs as lysergic acid diethylamide (L. S. D. 25). I should like to predict further that the introduction of these drugs marks the beginning of the eclipse of psychosurgery.

Dr. William P. Camp: Our experience to date at Norristown State Hospital is with 40 patients treated with chlorpromazine and 23 with reserpine. Our cases were mainly of manic-depressive psychosis in the manic stage, and of schizophrenia, though a few senile patients and patients with other psychiatric disorders were included in the group.

In the chlorpromazine series, 33 out of the 40 showed at least some improvement, 5 were unchanged, and 2 were worse. The usual dose of chlorpromazine is 300 mg. daily, with a range of 150 to 600 mg. per day. In five cases complications sufficiently severe to stop treatment were encountered (jaundice, hyperpyrexia, nausea, and vomiting). We have been following our chlorpromazine cases with serum bilirubin tests and a battery of liver function tests every two weeks.

Our experience with reserpine is less encouraging and more recent. Thirteen of 23 patients showed no improvement, and 1 was worse. However, we believe our doses of 7 mg. per day are not adequate, and we are using larger amounts at present. The only serious complications were those related to a prolonged lowering of blood pressure.

Our conclusions are that both drugs are effective in treating psychomotor overactivity symptomatically, and that chlorpromazine acts faster than reserpine. Neither medication should be used with depressive patients.

Dr. John W. Appel: It is my pleasure now to introduce some of our colleagues whose work in fields related to psychiatry, but separated from it, makes their comments of particular interest.

Dr. Carl Schmidt, Professor and Chairman of Department of Pharmacology, University of Pennsylvania School of Medicine: Psychopharmacology is a relatively new study, in

which the laboratory methods and animal study are of relatively little help. Empirically, some relationship between hypertension and psychiatric problems has been demonstrated—and here, of course, the rationale of the use of reserpine is clearer that that of chlorpromazine, which is essentially an antihistaminic. We do not know the connection between the physiologic actions of these drugs and their psychological reactions, but we are interested in finding out. This new field of psychopharmacology offers a fascinating prospect for research.

DR. J. S. HAFKENSCHIEL, Department of Internal Medicine, University of Pennsylvania: Reserpine is related to yohimbine and, unlike hydralazine (Apresoline) and other drugs which lower blood pressure, apparently does not produce arthritis or the collagen diseases. Depressions have been noted in cases in which reserpine is used to control blood pressure, but the extent to which this occurs and its significance have not yet been studied adequately.

DR. HENRY CORNMAN, Research Department, Smith, Kline & French Laboratories: Chlorpromazine was originally introduced with the idea that as a central nervous system depressant it could be used in modified sleep treatment. In animals it is a peculiar sedative in that it is not hypnotic, but blocks some conditioned reflexes. Clinically, it presents a therapeutic paradox in that the severe cases do best, the mild ones poorest; it is reported to work well with agitated alcoholics and has been suggested in multiple sclerosis. Possibly it produces a "medical lobotomy." More research is indicated, particularly in combination with other drugs, such as *d*-amphetamine (Dexedrine), lysergic acid, and reserpine.

DR. MANUEL PEARSON: The meeting is now open to discussion from the floor.

DR. WILLIAM E. HOLT: I should like to comment on some complications of treatment. Jaundice produced by chlorpromazine seems to be of the pseudo-obstructive type, and in one case appeared in 24 hours after the first dose was given. One patient with chlorpromazine developed an unexplained temperature of 104 F. In one case with severe mitral stenosis death followed the use of chlorpromazine, associated with tachycardia. In four patients receiving reserpine for hypertension agitated depressions occurred. Our observations on the electroencephalograms under chlorpromazine suggest that seizures in an epileptic might be increased by the medication, though, of course, some epileptics are helped by antihistamines. I should like to hear from anyone who has had experience with chlorpromazine in cases of epilepsy.

DR. HENRY BRILL, Assistant Commissioner of the Department of Mental Hygiene, Albany, N. Y.: I speak from observations made on 3000 cases in New York State Hospitals treated with chlorpromazine and/or reserpine. A very simple statistical measure of the effectiveness of a treatment of this sort is the amount of restraint necessary, which, of course, has to be recorded. In actual practice, the use of chlorpromazine has cut the amount in half. We have had very good results with its use in epileptics.

DR. N. W. WINKLEMAN JR.: In the past 19 months I have treated 550 patients with chlorpromazine and consider its chief value to be in facilitating other, more fundamental techniques of treatment, such as psychoanalysis.

DR. LESLIE R. ANGUS: At the Woods Schools, we have treated approximately 50 hyperkinetic and emotionally disturbed children with reserpine and chlorpromazine—about one-half with one and one-half with the other, and some in combination. Doses have been smaller than those now reported, but there have been no complications. Results indicate symptomatic improvement in approximately one-half the cases, with no appreciable difference in the effects of the two drugs and no improved effect by using the two together. At least two cases showed the paradoxical psychological reaction mentioned by others here. We consider the investigation well justified and plan to continue it.

DR. MANUEL PEARSON: To summarize the presentations: We have the pooled experience with the use of chlorpromazine and reserpine in approximately 4000 cases of various psychiatric disorders. In general, the results have been encouraging clinically. Pharmacologically, we still have a great deal to learn, and further investigations should prove helpful. From the psychiatric point of view, there seems to be a general agreement that these drugs are of value in dealing with psychomotor overactivity and agitation, without distorting fundamental thinking or feeling processes and without altering the ego structure. Thus, they are of great potential value in establishing a psychotherapeutic relationship and in facilitating psychotherapy. Clearly, we do not know enough about dosage and specific indications, or about the possible complications. Enough has been said, however, to warrant further clinical investigation, the results of which we might hope to discuss at some future meeting.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

SUBSTRATE SPECIFICITY OF BRAIN HEXOKINASE. A. SOLS and R. K. CRANE, J. Biol. Chem. **210**:581, 1954.

Sols and Crane have examined the substrate specificity of particulate cerebral hexokinase on the Michaelis constant and maximal phosphorylation rate of substituted or modified carbon atoms of glucose. Sixteen compounds, including 5- and 7-carbon sugars and nonreducing compounds, have been found to be phosphorylated, although their suitability as substrate for brain hexokinase varies over a wide range. Five compounds have been found that act as competitive inhibitors. The data support the conclusion that the specificity of brain hexokinase involves the ring structure and the hydroxyl groups at carbon atoms 1,3,4, and 6 of the glucose molecule.

PAGE, Cleveland.

NON-COMPETITIVE INHIBITION OF BRAIN HEXOKINASE BY GLUCOSE-6-PHOSPHATE AND RELATED COMPOUNDS. R. K. CRANE and A. SOLS, J. Biol. Chem. **210**:597, 1954.

Noncompetitive inhibition by glucose-6-phosphate and related compounds was studied with respect to the specificity of purified particulate preparations of cerebral hexokinase. A comparison of the structures of 25 compounds, 6 of which are inhibitors, supports the conclusion that the formation of the enzyme-inhibitor complex involves the pyranose ring structure, the hydroxyl groups at carbons 2 and 4, and the phosphate group at carbon 6. The data indicate that brain hexokinase possesses, in addition to the binding sites for substrates and adenosinetriphosphate, a third specific binding site, for glucose-6-phosphate.

PAGE, Cleveland.

SEROTONIN AND ITS METHYLATED DERIVATIVES IN HUMAN URINE. F. M. BUMPUS and I. H. PAGE, J. Biol. Chem. **212**:111, 1955.

Evidence has been presented by Bumpus and Page that bufotenin and N-methyl serotonin, as well as serotonin itself, appears in normal human urine. Bufotenin appears to be a hallucinogen, and therefore the appearance of these indole derivatives in human urine is of especial interest.

PAGE, Cleveland.

Neuropathology

CHANGES IN THE CENTRAL NERVOUS SYSTEM FOLLOWING IRRADIATION WITH 23 MEV X-RAY FROM THE BETATRON. A. ARNOLD, P. BAILEY, R. A. HARVEY, L. L. HAAS, and J. LAUGHLIN, Radiology **62**:37 (Jan.) 1954.

The authors point out that the general feeling in the past has been that nerve tissue is relatively radioresistant and that it can tolerate considerable exposure to x-rays with very little ill effect. It has been thought that most of the damage done has come from occlusion of blood vessels by the irradiation rather than from a direct effect upon the nerve tissue itself. Arnold and his associates disagree with both these postulates. From their experience with treatment of brain tumors by x-rays and from experimental work, the authors believe that the central nervous system of both monkeys and man is more radioresponsive than has been generally supposed. They believe, further, that the white matter of the central nervous system is selectively radiosensitive, but that the necrosis which occurs in the white matter is usually a delayed necrosis unless the dose is very large. In the experiments of the authors the brains of living monkeys were treated with a collimated beam of 23-mev x-rays generated by the betatron. The beam size was 1 or 2.5 cm. in diameter, and the beam went through the brain either transtemporally or transfrontally. The exit dose was approximately equal to the entrance dose, so that the entire region of the brain irradiated was irradiated approximately to the same degree. Large single doses produced an acute necrosis of the entire area of the brain which was treated. In the dose range of 5000 to 7000 r the acute pathologic findings were inflammatory reactions, edema, myelin injury, hemor-

rhage, and some small areas of acute necrosis. The monkeys showed extensive clinical evidence of irradiation, such as quadriplegias, seizures, and impairment of consciousness. The inflammatory responses, edema, and hemorrhages slowly resolved; the clinical seizures subsided, and a normal state of alertness returned. About four months after irradiation progressive neurologic disorders appeared rather abruptly. Pathologic examination of the brains revealed that extensive non-selective radionecrosis had occurred throughout the entire path of the x-ray beam, and only in the path of the x-ray beam. Monkeys that were treated with a dosage range from 3000 to 5000 r had similar but less severe acute symptoms and after a longer intermediate normal period. The delayed radionecrosis occurred six to eight months after treatment. Pathologic examination at this time showed intense inflammatory reactions, hemorrhages, myelin damage, and edema throughout the irradiated part of the brain. The disintegration of the white matter began as a demyelinating process and progressed to an actual necrosis of the white matter constituents.

Arnold and his associates believe that comparable radiation effects are being observed in their patients who are receiving x-ray therapy. Aggravation of symptoms is common during the period of treatment. Relatively asymptomatic periods are common following treatment. The authors are attempting to determine specific tumor doses which will inhibit or destroy the various tumors of the brain without producing the delayed necrosis.

WEILAND, Grove City, Pa.

HISTOPATHOLOGY AND PATHOGENESIS OF CEREBRAL ARTERIAL ANEURYSMS. A. E. WALKER and G. E. ALLEGIE, Rev. neurol. **86**:477, 1953.

Walker and Allegie attempt to demonstrate that local vascular degeneration plays a greater role in the formation of aneurysms than is generally recognized. The study is based on 39 cases, with ages ranging from 29 to 72 years. Death was attributable to rupture of the aneurysm in 35 cases and to other causes in 4 cases. Hypertension was present in 18 cases and generalized arteriosclerosis in 21. Other anomalies, such as polycystic kidney and vertebral angioma, were observed in nine cases.

Arteriosclerosis of the vessels at the base of the brain was evident in 13 cases. Of 29 vessels studied histologically, 25 had severe atheromatous changes. In all but one instance there was a proliferation of the intima and either disruption or dissolution of the elastic layer. In 13 cases the wall of the aneurysmal sac contained fragments of elastic tissue, and at times muscle fibers, suggesting a dilatation of the vessel and subsequent degeneration.

BERLIN, New York.

Meninges and Blood Vessels

MEASLES MENINGOENCEPHALOMYELITIS. W. F. TWINING MCMATH, Brit. M. J. **2**:789 (Oct. 2) 1954.

The protean character of measles meningoencephalitis and its tendency to occur in small groups are well illustrated in a series of 10 cases of the disease, 3 of which occurred in the preeruptive stage, encountered in a localized area of northwest London between September, 1951, and June, 1953. Analysis of these 10 cases, which Twining McMath briefly presents, failed to elucidate the pathogenesis, prophylaxis, or treatment of this complication. The author believes that failure of corticotropin to influence the course of the disease in two cases supports the hypothesis of a virus rather than an allergic etiology. There appeared to be no correlation between the incidence and severity of the disease and the character of the primary lesion. There was one death in the series. None of the nine patients who recovered had physical residua, but two of them showed mental deterioration.

ECHOLS, New Orleans.

THE BLOOD-C. S. F. BARRIER TO BROMIDE IN DIAGNOSIS OF TUBERCULOUS MENINGITIS. L. M. TAYLOR, H. V. SMITH, and G. HUNTER, Lancet **1**:700 (April 3) 1954.

Since early diagnosis of tuberculous meningitis is one of the chief factors in the prognosis, the authors have attempted to find some test which will be of help in the early stages of this disease. They have found that the ratio of blood serum bromide to the C. S. F. bromide level is altered early in tuberculous meningitis. Normally the blood serum contains two or three times as much bromide as does the C. S. F. (after sodium bromide is given either orally or intravenously), giving a bromide ratio of 2:3. During the intrathecal tuberculin reaction, i. e., the wave of meningitis which follows the introduction of tuberculin into the C. S. F. of a Mantoux-positive person, there is a dramatic effect on the passage of bromide from the blood to the C. S. F. The ratio falls to unity; in other words, the blood-C. S. F. barrier to bromide is abolished.

Active tuberculous meningitis appears to have the same effect on the blood-C. S. F. barrier as does the intrathecal tuberculin reaction. The ratio is profoundly depressed but returns to normal when the infection is brought under control. In other varieties of nonpurulent meningitis, including poliomyelitis, choriolymphocytic meningitis, neurosyphilis, and cerebral abscess, there was little change in the bromide ratio, although the cell content and protein level of the C. S. F. were similar to those in tuberculous meningitis. Intrathecal streptomycin in the nontuberculous group had no obvious effect on the bromide ratio.

The authors point out that, although a low bromide ratio is not pathognomonic of tuberculous meningitis (it is seen, e. g., in spinal block), in doubtful cases where the picture as a whole is compatible with the diagnosis of tuberculous meningitis, the finding of a low bromide ratio is strong reason for beginning treatment without delay.

MADOW, Philadelphia.

Diseases of the Brain

MENINGIOMAS WITHIN THE LATERAL VENTRICLES. A. E. WALL, J. Neurol., Neurosurg. & Psychiat. **17**:91, 1954.

Wall presents a clinical survey of eight meningiomas with origin from the choroid plexus or velum of the lateral ventricles seen in a five-year period. He has collected some 50 others from the literature. A clinical syndrome characteristic of these tumors is difficult to delineate. The symptoms—increased intracranial pressure with headache; contralateral visual field defects, varying from visual inattention to homonymous hemianopsia; contralateral sensorimotor hemiparesis, and paralexia increased by surgery (because most tumors occur in the left hemisphere)—can be caused by any glioma in the region of the trigone. The cerebellar signs, also mentioned by Cushing and Eisenhardt, are difficult to interpret in the light of the hemiparesis and are present in only about a quarter of the cases. Facial paresthesias on the same side as the lesion can occur. Plain skull x-rays, spinal fluid determination, and the EEG are of little diagnostic help. (In one case in Wall's series the EEG was of value in localizing the lesion to the supratentorial region, and in one case calcification in the tumor was visualized.) Ventriculography is the most reliable diagnostic aid. Carotid angiography in half the cases demonstrated an enlarged anterior choroid artery which ended posteriorly in a small tangle of vessels near where the anterior inferior extremity of the tumor lay in the temporal horn. Vertebral angiography in lateral views revealed a constant defect: absence of the normal choroid plexus pattern and the probability of lack of filling of the opposite plexus. The posterior choroidal vessels may be abnormally numerous or stretched.

In the author's opinion the differentiation is artificial between true choroid plexus meningiomas lying wholly within the lateral ventricle and those of the velum tending to lie partly within the ventricle and partly embedded in the hemisphere. Wall also has found that the pathological type consists of both meningiotheliomatous and fibrous features, rather than being predominantly fibrous, as suggested in the literature.

BERRY, Philadelphia.

METABOLIC DISORDERS IN HEAD INJURY. G. HIGGINS, W. LEWIN, J. R. P. O'BRIEN, and W. H. TAYLOR, Lancet **1**:61 (Jan. 9) 1954.

The authors report the metabolic disturbances noted in a group of 76 consecutive patients wih major closed head injuries who remained unconscious for more than 12 hours after injury and required pernasal intragastric tube feeding. The patients were divided by biochemical criteria into three groups: Group I contained those patients for whom biochemical investigations remained normal from the time of injury to the time of recovering consciousness; Group II consisted of patients who showed transient biochemical abnormalities which disappeared spontaneously without specific therapy, and Group III included those patients who, in addition to transient abnormalities, showed severer biochemical disturbances which were persistent and progressive unless reversed by specific treatment. Group I contained eight patients, none of whom died. Group II contained 50 patients, 12 (24%) of whom died. In this group, 32 had proteinuria, 22 had an elevated blood urea level, and 22 had lowered total plasma protein levels. In Group III there were 18 patients, of whom 11 (61%) died. Nine of the patients had hyperchloremia and hypochloruria, and three of these died. Five patients had hypochloremia and hyperchloruria, and three of these died. Three developed renal uremia, and all died. Two had unequivocal evidence of respiratory alkalosis, and both died.

In the entire group, about half the deaths took place during the first 5 days, but thereafter the longer the duration of coma the smaller the proportion of deaths up to a period of about 40 days, after which the mortality increased considerably. There was a higher mortality with increasing age.

The authors discuss the treatment required for these metabolic disturbances, as well as a regimen of fluid therapy in the management of the unconscious patient.

MADOW, Philadelphia.

Diseases of the Spinal Cord

LUMBAR AND SACRAL CYSTS OF MENINGEAL ORIGIN. K. J. STRULLY and S. HEISER, Radiology **62**:544 (April) 1954.

Strully and Heiser present histories of five patients thought to have lumbar and sacral meningeal cysts. In four of these cases the diagnosis was verified by operation. The fifth patient refused operation. In addition, a sixth case is reported in which a perineurial cyst was demonstrated in the sacral area by a myelogram and proved to exist by surgical operation. In all of the six cases lumbar myelograms were performed and found to be abnormal, with filling of the cysts in all the myelographic studies. The clinical symptoms did not conform to a typical pattern for meningeal cysts. In most cases the patients had low back pain which was not typical of ruptured intervertebral disc or of any of the other commoner causes of low back pain.

Strully and Heiser believe that surgical intervention should be seriously considered where a meningeal or perineurial cyst is suspected, even though a myelogram may not furnish proof of its existence. When a patient with low back pain has surgical exploration for a ruptured intervertebral disc and none is found, the cause of the patient's complaints may sometimes be demonstrated by unroofing the sacrum. Some lesions of the sacral canal may be demonstrated by no other method than surgical exploration.

WEILAND, Grove City, Pa.

COLLAGENOUS CHANGES IN THE INTERVERTEBRAL DISK WITH AGE AND THEIR EFFECT ON ITS ELASTICITY. A. NAYLOR, F. HAPPEY, and T. MACRAE, Brit. M. J. **2**:570 (Sept. 4) 1954.

Naylor and associates, using x-ray crystallographic methods, made a study of the collagenous changes in the human intervertebral disks with age. The x-ray diffraction diagrams they obtained proved that the elasticity of the annulus fibrosus is dependent upon the orientation and mobility of the collagen fibrils, properties which decrease with advancing age after the third decade. The diagrams of the nucleus pulposus show that increased orientation and ultimate crystallization of the collagen occur with advancing age. This indicates loss of gel structure, which accounts for impaired elasticity. The reduced elasticity of the intervertebral disk with age can be explained by the combination of these factors.

ECHOLS, New Orleans.

Peripheral and Cranial Nerves

ALOPECIA, OPTIC ATROPHY, AND PERIPHERAL NEURITIS OF PROBABLY TOXIC ORIGIN. W. J. C. SYMONDS, Lancet **2**:1338 (Dec. 26) 1953.

Symonds reports the case of a 59-year-old housewife who developed loss of vision, loss of hair, and pains in her legs following a luncheon given for her family. About 12 hours after the meal she began to vomit and had diarrhea and abdominal colic. These symptoms continued for two days and were followed by nausea and anorexia for a week. At about this time the hair of her scalp and eyebrows fell out progressively, until she was completely bald. Sixteen days after the meal she developed tingling and shooting pains in her feet, hands, and scalp. Examination showed complete alopecia of the scalp and eyebrows and hyperesthesia of the toes with sluggish deep tendon reflexes in the legs.

Examination of the cerebrospinal fluid revealed no abnormalities. Thallium poisoning was diagnosed, although examination of the urine and feces and muscle biopsy revealed no trace of this metal, and she was given a course of dimercaprol. The pains began to regress during the next few days, but her vision started to deteriorate. After another two weeks her visual acuity began to improve and her hair to grow again but she became depressed. She had one relapse with recurrence of the same symptoms one year later, and with another course of dimercaprol the pains in the legs disappeared and her hair started to grow but the vision did not improve.

One son had similar symptoms following the luncheon, including general lassitude, aching in his legs, and alopecia. A maid working in the patient's home also had a short attack of diarrhea and vomiting, followed by loss of hair.

The author reviews the effects of thallium poisoning, which include alopecia, visual disturbance, and mental disturbances. He concludes that this syndrome may result either from thallium poisoning or from some other toxic cause, at present unidentified.

MADOW, Philadelphia.

Treatment, Neurosurgery

PROBLEM OF EVALUATING TREATMENT OF PROTRUDED LUMBAR INTERVERTEBRAL DISK. C. H. MILLIKAN, J. A. M. A. **155**:1141 (July 24) 1954.

Because of the practical need for knowledge about the comparative results of conservative and operative treatment of protruded lumbar intervertebral disk, Millikan made a long-time study of two groups of patients: (1) those treated conservatively and (2) those treated surgically (with or without fusion of the involved area of the spinal column).

A follow-up study comparing and evaluating results of the two types of therapy in 429 patients with a protruded lumbar intervertebral disk showed that in two respects, ability to return full time to the former occupation and the number of attacks occurring after treatment, surgical treatment was more effective than conservative treatment.

The author states that surgical treatment is probably indicated under the following conditions: when there is progressive paralysis or sensory loss; when an extremely severe, protracted attack of sciatica does not respond to conservative treatment; when there are repeated attacks of sciatica, with the production of considerable incapacity; when there is failure to improve during an adequate trial of conservative treatment, or when the patient cannot afford, for economic reasons, to continue conservative treatment for an indefinite period of time.

ALPERS, Philadelphia.

ELECTROTONIC TREATMENT IN DEMENTIA PARALYTICA. M. C. PETERSEN, J. Nerv. & Ment. Dis. **118**:162 (Aug.) 1953.

In a seven-year period 70 patients with dementia paralytica received a total of 1120 electroshock treatments for the associated psychological disturbances. Forty-two were improved; 21 were slightly to moderately improved and 7 were unimproved. Of 33 patients with no recent fever therapy or chemotherapy, cell counts were lowered in 27 and total protein lowered in 18 following electroshock treatment.

The E. C. T. was administered because of psychological disturbances in the form of hallucinations, agitation, depression, resistiveness, refusal to eat, and paranoid ideation. Following treatment, the patients became cooperative and relaxed and gained weight. Specific antisyphilitic therapy was also administered to all these patients.

BERLIN, New York.

Encephalography, Ventriculography and Roentgenography

LOCALIZATION OF INTRACRANIAL NEOPLASMS WITH RADIOACTIVE ISOTOPES. W. B. SEAMAN, M. M. TER-POGOSSIAN, and H. G. SCHWARTZ, Radiology **62**:30 (Jan.) 1954.

Seaman and his associates analyzed 200 cases in which they used radioactive diiodofluorescein in an attempt to localize brain tumors. Of this group, 65 patients were proved to have brain tumors by operation or by autopsy. Correct localizations were obtained by the method in 30 of these 65 patients, an accuracy of 46%. Twenty intracerebral lesions other than neoplasm (hematomas, aneurysms, and abscesses) were also localized by the method. Subtentorial tumors prove very difficult to localize. The accuracy in this region was only 27%, as compared with an accuracy of 50% for the supratentorial tumors. Cystic and necrotic tumors are difficult to localize. Such tumors do not concentrate the radioactive material sufficiently for localization. The authors feel that this technique is a useful screening procedure to aid in the selection of patients for further diagnostic studies.

WEILAND, Grove City, Pa.